Studies Towards A Total Synthesis of Roseophilin

A Thesis Submitted for the Degree of Doctor of Philosophy

by

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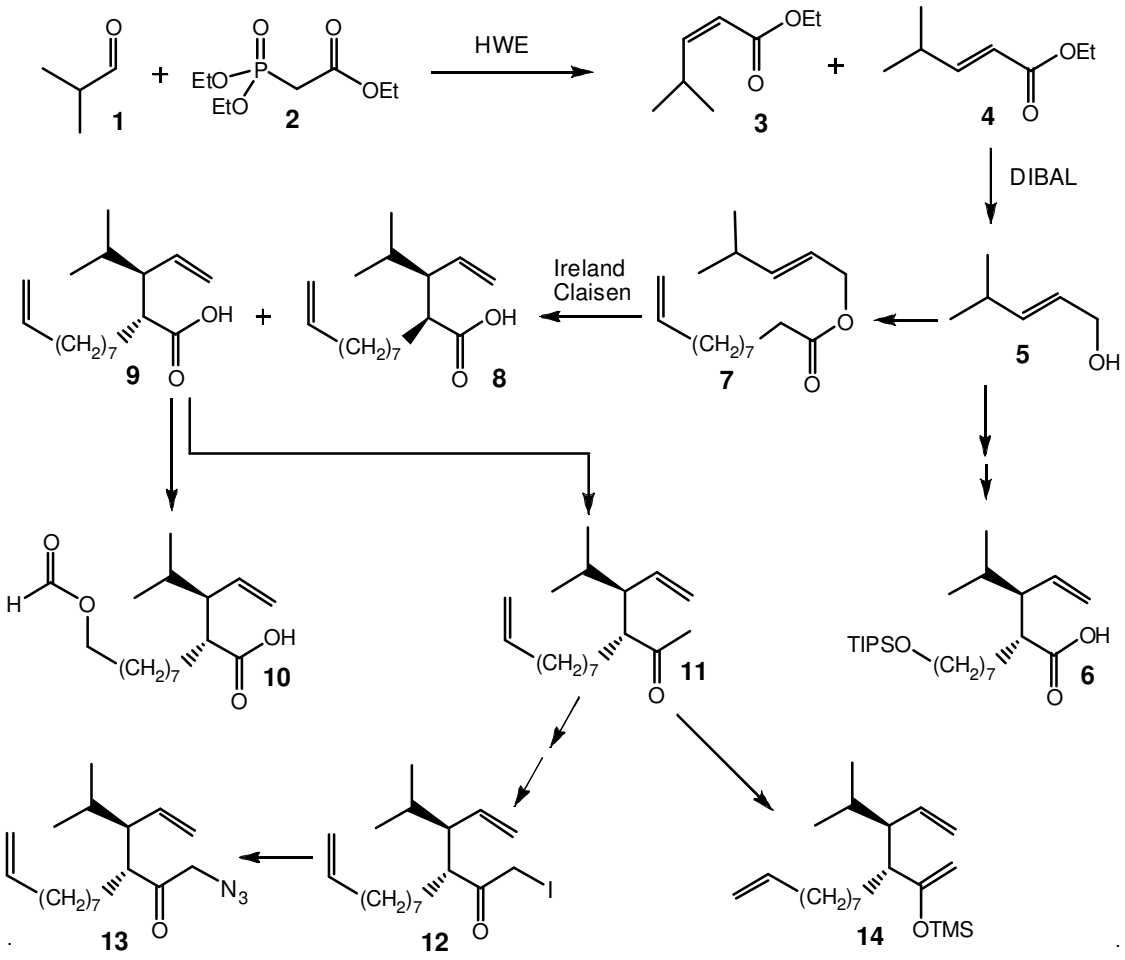
I, Barry David Glyn Haylor, hereby declare that this thesis has not been and will not be submitted, in whole, or in part to another University for the award of any other degree

Signed _____

Abstract

Re-investigation of the the published[1] route to **6** is described. Investigation and optimization of the preparation of **4** *via* a highly *E*-selective Horner Wadsworth Emmons (HWE) reaction, and optimization of its reduction to **5,** enabling the preparation of **5** in quantities of tens of grams is described. Preparation of **7,** its conversion to **8** and **9** via an Ireland-Claisen rearrangement, optimization of this rearrangement, and investigation of methods of separation of **8** and **9** are described. Preparation of **10**, **11**, **12**, **13**, and **14** are described. Investigation of a number of methods of cyclization of **12**,**13** and **14** are described. All compounds described are racemic.



1) Viseux E.M.E. Synthetic Studies Towards a Total Synthesis of Roseophilin. D. Phil. Thesis, University of Sussex, January 2005.

Acknowledgements

First and foremost I should like to thank my supervisor, Professor P.J. Parsons for the opportunity to work in his research group. I also should like to thank Dr C. Penkett for his support in the role of co-supervisor, and my colleagues in Laboratory Ar301 for their company over the last three years. I should also like to thank Mr M. Paradowski and Professor S. Ward for allowing me the use of their laboratory for my final couple of months' practical work. Thanks are due also to Mr M. Henry for all sorts of help and advice, Mr C. Dadswell for his invaluable assistance with the GC, Dr I. Day for his incredible patience with my questions on NMR, Dr A. Abdul Sada for similar patience and assistance with mass spectrometry, and finally to Dr J. Woolford for his many helpful suggestions with respect to this thesis.

Contents

Abbreviations

AIBN	azo*bis*isobutyronitrile
aka	also known as
Bn	benzyl
Bz	benzoyl
n-BuLi	*n*-butyl lithium
Boc	*t*-butoxycarbonyl
BSA	*N*,*O*-*bis*-(trimethylsilyl)acetamide
BSTFA	*N*,*O*-*bis*-(trimethylsilyl)trifluoroacetamide
Comin's Reagent	*N,N*-*bis*(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine
CDI	carbonyl diimidazole
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	dichlorodicyanobenzoquinone
dehydr.	dehydrated
DIBAL	di-isobutylaluminium hydride
DIPEA	di-isopropylethylamine, Hünigs base
DMAP	4-dimethylaminopyridine
DMH	*N,N*-dimethylhydrazine
dppp	1,3-*bis*(diphenylphosphino)propane
dppe	1,2-*bis*(diphenylphosphino)ethane
DR	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
ee	enantiomeric excess
GC	gas/liquid chromatography
GC-MS	gas/liquid chromatography using a mass spectrometer as the detector.
HFIP	1,1,2,3,3,3 hexafluoroisopropanol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
hr, hrs	hour(s)
HWE	Horner Wadsworth Emmons Reaction
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
mCPBA	m-chloroperoxybenzoic acid
mol	moles
MOM	methoxymethyl
MOMCl	chloromethyl methyl ether
MsCl	methanesulfonyl chloride

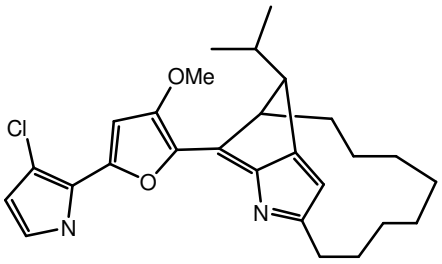
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMMO	*N*-methylmorpholine-N-oxide
$Pd_2(dba)_3$	*tris*(dibenzylidene acetone)dipalladium(0)
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
pTSA	*p*-toluenesulfonic acid
rt	room temperature
RCM	ring-closing metathesis
SEM	2-(trimethylsilyl)ethoxymethyl
SEMCl	2-(trimethylsilyl)ethoxymethyl chloride ('SEM-chloride')
TBAF	tetrabutylammonium fluoride.
TBDMSCl	chloro dimethyl (*t*-butyl) silane ('TBDMS chloride')
TBDMSTf	*tert*-butyldimethylsilyltrifluoromethanesulfonate ('TBDMS triflate')
Tf	triflate, trifluoromethanesulfonate,SO_2CF_3
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	chlorotriisopropylsilane ('TIPS chloride')
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate ('TIPS Triflate')
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane ('TMS chloride')
$TMSCHN_2$	trimethylsilyldiazomethane
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl, (tosyl)

Chapter 1 Introduction

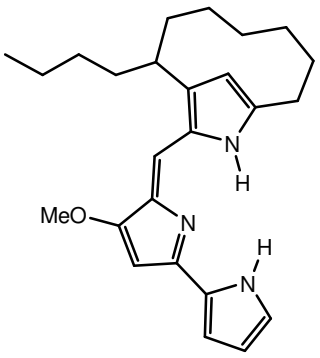
1.1 Discovery and Investigation of Roseophilin

Roseophilin **1** was first isolated from the actinomycete S*treptomyces griseoviridis* and identified as a cytotoxic agent, active against human erythroid leukaemia cells and KB human epidermoid carcinoma cells. Its existence and structure (determined primarily from NMR data) was published by Seto and co-workers[1] in 1992. Its pharmacology is particularly unusual, in that the synthetic unnatural enantiomer was shown[2] to be more potent that the natural one. It has been shown[3] to be an inhibitor of certain protein phosphatases, but its exact mode of action remains unknown, and it is regarded as too toxic for clinical use.[4]

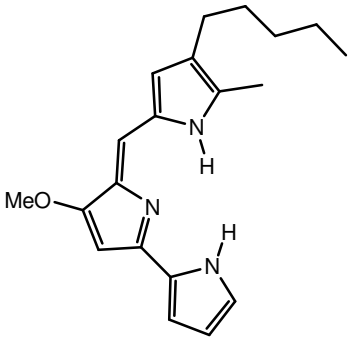
The name roseophilin is derived from its red colour, and its unique structure is most closely related to the prodigiosin alkaloids *(e.g.* **2, 3, 4,** see Figure 1) produced by other strains of *Serratia* and *Streptomyces*, which not-uncommonly grow in red colonies on starchy media.[4]



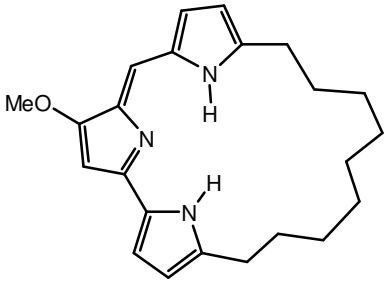
Roseophilin **1**



'Streptorubin B' **2**



'Prodigiosin' **3**



'Nonylprodigiosin' **4**

Figure 1

The parent organism S*treptomyces griseoviridis* (also designated as *Streptomyces K61*) has been approved both in the US[5] and EU[6] as a biopesticide for use against fungal diseases of plants.

Roseophilin has attracted much attention over the 20 years since its discovery, owing to its potential in cancer treatment, and to its unique structure. The latter makes it a particularly interesting and challenging synthetic target.

1.2 Syntheses and Approaches to Synthesis

Retrosynthetically, the molecule **1** may conveniently be divided into an aromatic side-chain (Carbons 1-8, Seto's numbering, Figure 2) and the tricyclic portion (Carbons 9-22, highlighted in red in Figure 2) derived from **5** (usually referred to as 'the core'), first synthesized by Fűrstner.[7]

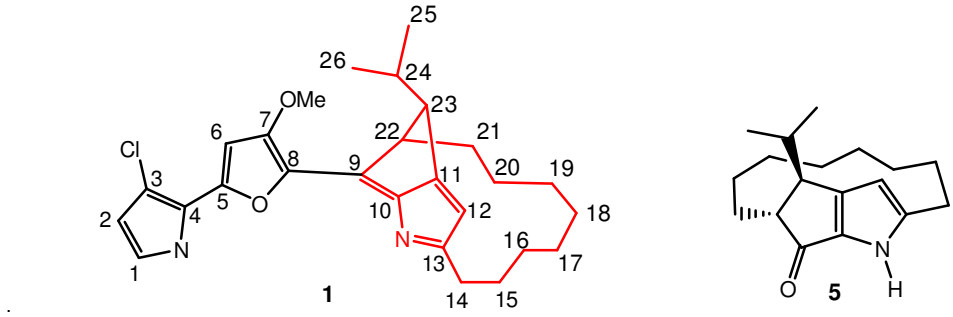


Figure 2

The core is a fused bicyclic system, with an 8-carbon *ansa*-bridge, and all synthetic strategies to date start with the same initial disconnection, *i.e.* removal of the side chain from the core, leaving a ketone for reconnection. With the publication of Fűrstner's full total synthesis,[8] any synthesis of the core **5** becomes (by convention) a formal total synthesis, and therefore the (topologically most-interesting) core becomes the 'real' target for synthesis.

To date there have been three total syntheses, and eleven formal total syntheses published. These are presented in 'timeline' format overleaf (Table 1). This shows total and formal total syntheses, and significant models and approaches to the synthesis.

The molecule has a number of attractive features as a synthetic target. The 8-carbon bridge is part of a 13-carbon macrocycle, but the bridge itself is not functionalised. This leaves the chemist with the option of disconnecting it wherever convenient, with the obvious proviso that any functional groups left over from the connection are removable.

The bicyclic portion is conformationally rigid, and this, and the presence of the isopropyl group, makes the molecule slightly strained. This factor is particularly important for the closure of the macrocycle, and has had a large influence on synthetic strategies.

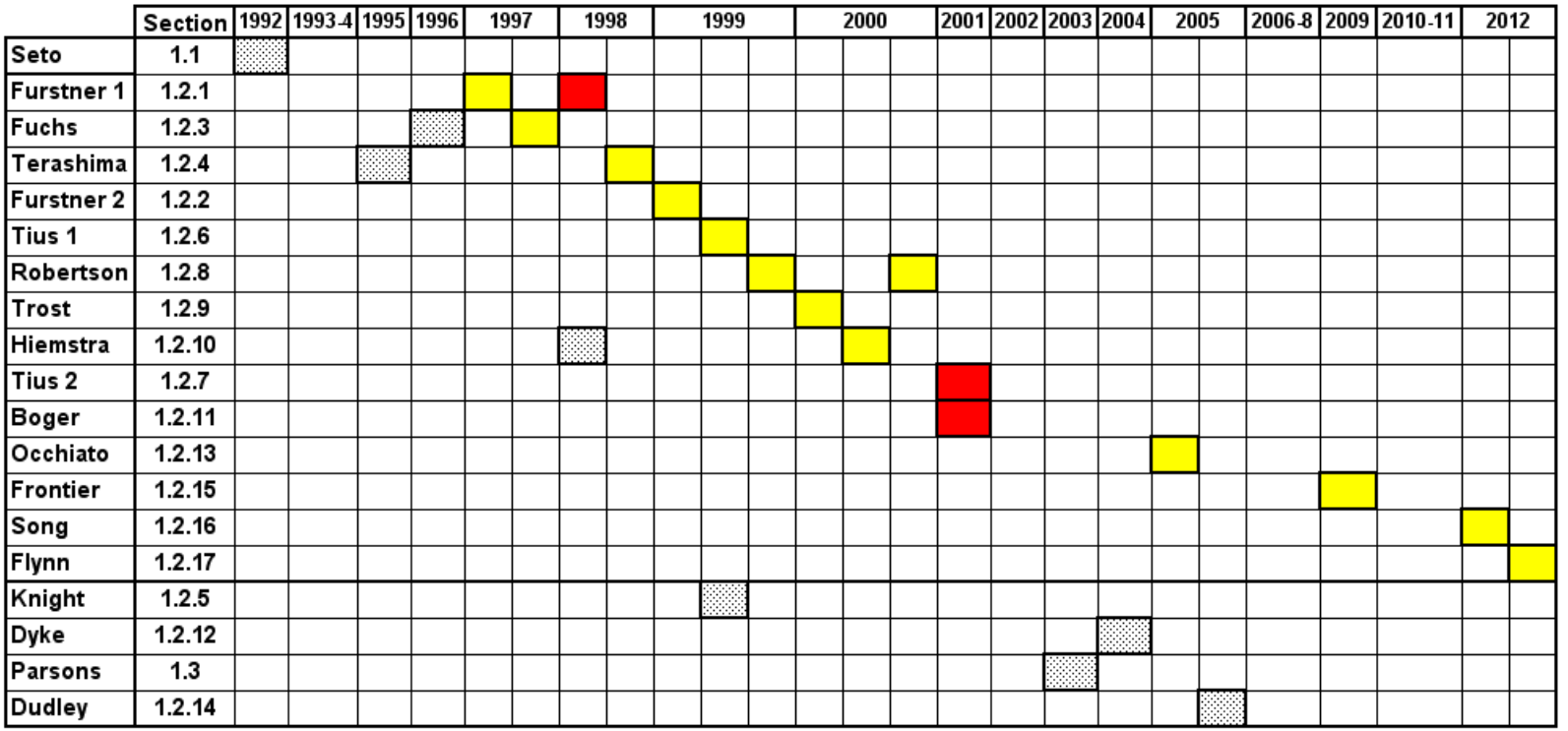

Section
1992
1993-4
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006-8
2009
2010-11
2012
Seto 1.1
Furstner 1 1.2.1
Fuchs 1.2.3
Terashima 1.2.4
Furstner 2 1.2.2
Tius 1 1.2.6
Robertson 1.2.8
Trost 1.2.9
Hiemstra 1.2.10
Tius 2 1.2.7
Boger 1.2.11
Occhiato 1.2.13
Frontier 1.2.15
Song 1.2.16
Flynn 1.2.17
Knight 1.2.5
Dyke 1.2.12
Parsons 1.3
Dudley 1.2.14
Total Synthesis
Formal Total Synthesis
Other significant publication

Table 1

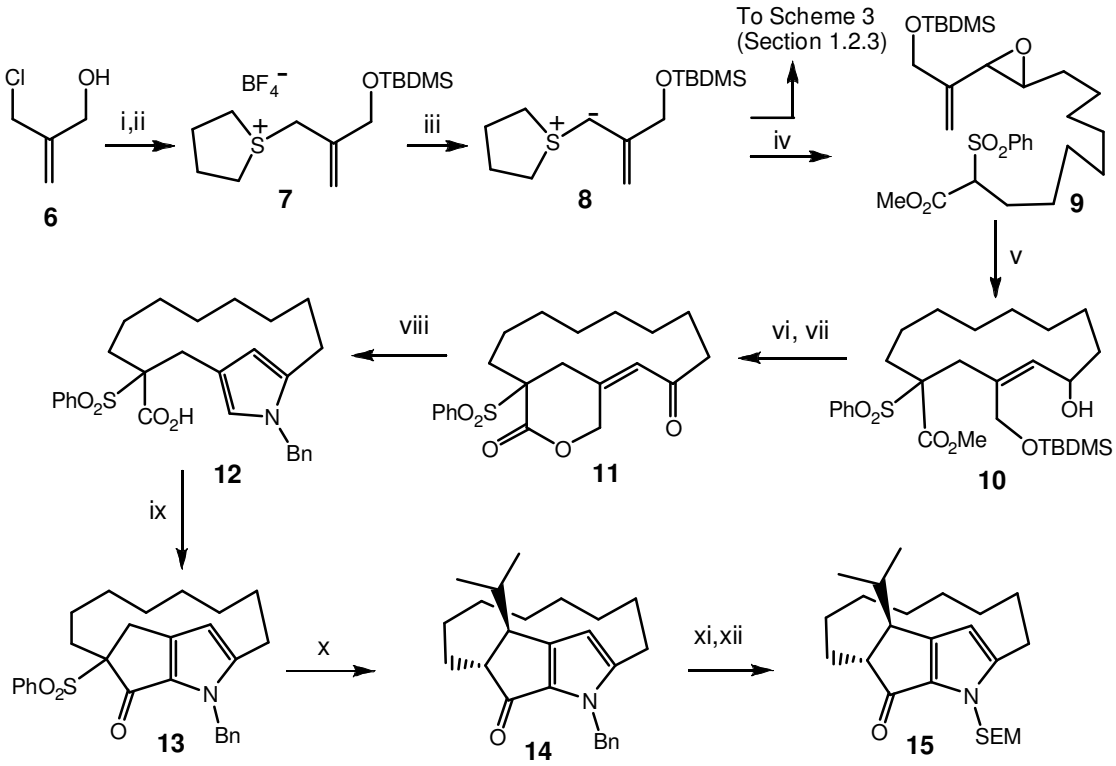
A RCM protocol using Grubbs' catalyst[9] (necessarily followed by hydrogenation of the resultant double bond) at any point in the 8-carbon *ansa*-bridge is inviting, however the work of Fuchs (see 1.2.3) showed that the degree of strain in the bridge is sufficient to prevent effective RCM with the central, bicyclic portion complete (and flat), unless other factors are present to assist the process, such as the incorporation of bulky groups to bring the ends of the open-chain precursor into closer proximity.[10] In other cases, closure of the macrocycle was performed prior to closure of the cyclopentenone and/or pyrrolidine rings, or with the central bond of the bicyclic portion saturated[11] in order to bend the bicyclic portion.

In addition to this, the presence of the bulky isopropyl group at C-23 adds additional strain and requires careful consideration of stereochemistry in the synthesis.

The various syntheses, including the published model studies, will now be considered in more detail, primarily from the point of view of their overall synthetic strategy. They are presented in approximate chronological order, although this is varied where a synthesis is a derivative of a previous one. The work done in this department is placed out of sequence (see 1.3) for convenience, and is treated in greater detail. It includes published and unpublished material and the current project is derived from it.

1.2.1 Fürstner's 1st Total Synthesis (racemic) – 1997 & 1998

The synthesis of the 'Core' (Scheme 1) was published[7] by Fürstner and Weintritt in 1997, followed by the complete synthesis[8] in 1998.



i) TBDMS-Cl, DBU, DCM, 1h, rt, 90%; ii) a) NaI, acetone, reflux; b) tetrahydrothiophene, $AgBF_4$, rt, 73%; iii) *t*-BuLi THF -78° iv) a) 9-bromononanal 84%; b) KH, methyl-phenylsulfonyl acetate, rt, DMF, 85%; v) Cat. $Pd(PPh_3)_4$, DPPE, THF, reflux, 85%; vi) TBAF, NH_4F, THF, rt, 63%; vii) Dess Martin periodinane, DCM, 83%; viii) $BnNH_2$, Pd $(PPh_3)_4$, THF, rt 70%; ix) a)1-chloro-2-methyl-propenyl dimethylamine, DCM; b) $SnCl_4$, 1,2-dichloroethane, 76% (2 steps); x) *i*-$PrMe_2ZnMgCl$, *t*-BuOK, 0°, 51%; xi) a) Ca/liq. NH_3; b) pyridinium dichromate, DCM, 50% (2 steps); xii) KH, SEM-Cl, DMF, rt 81%

Scheme 1

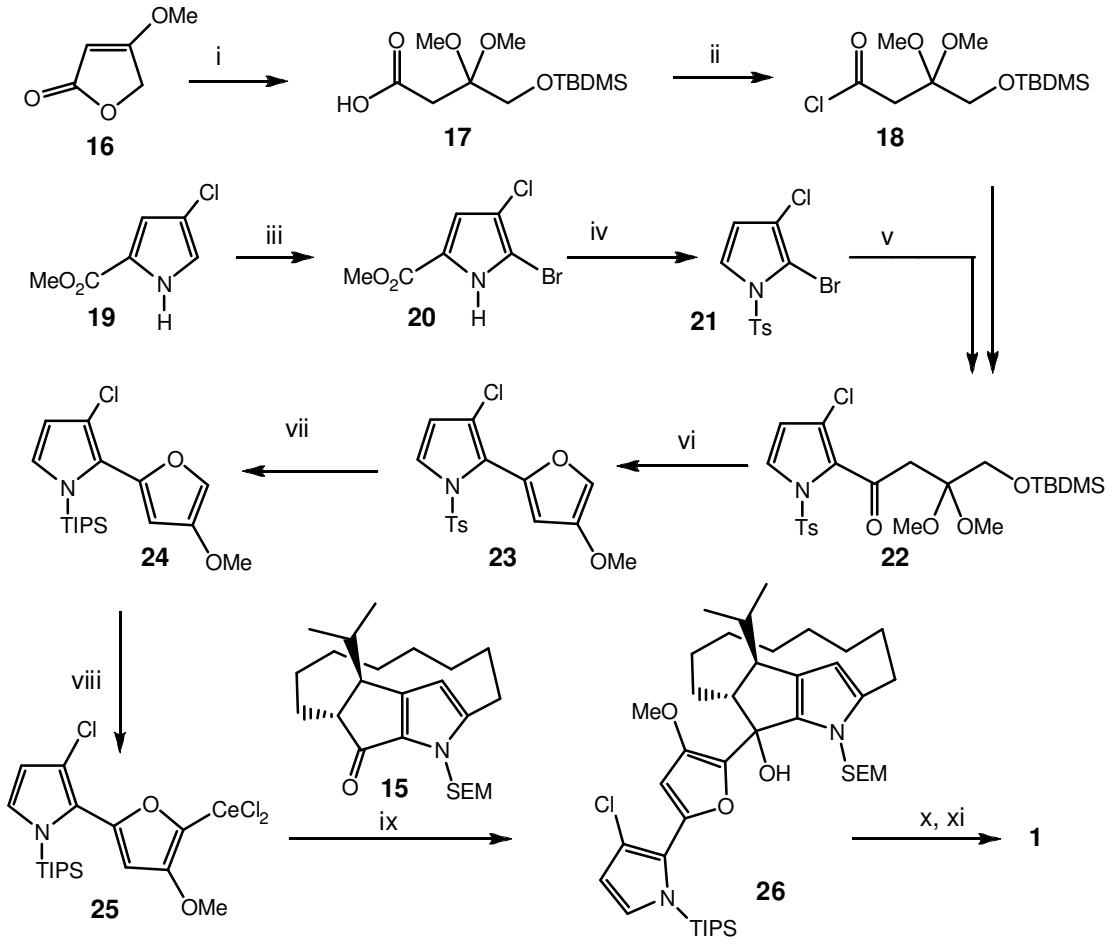
The first synthesis by Fűrstner, unlike many of its successors, did not use the RCM approach, but relied heavily upon palladium chemistry instead. The macrocycle was closed first (Scheme 1, step *v*) *i.e.* in a condition of minimum strain, prior to formation of either of the smaller rings. Macrocyclization was effected by attack of the β-sulfonyl ester (as an internal nucleophile) upon the vinyl epoxide, in the presence of a Pd(0) catalyst, leaving the molecule neatly set-up for closure of the two five-membered rings.

The bulky isopropyl group was introduced last using a mixed zincate *i*-$PrMe_2ZnMgCl$. This was made *in situ* from $ZnCl_2$. TMEDA, 2 equivalents of MeLi, and *i*-PrMgCl, and used in the presence of *t*-BuOK. The *t*-BuOK eliminates $PhSO_2H$, to give an αβ-unsaturated ketone, to which the zincate then adds Michael fashion. The

stereochemistry of this addition is controlled by the presence of the bridge, which shields the double bond from attack on the undesired side. This late addition of the isopropyl group is unique amongst the published syntheses, however it does add to the significance and synthetic potential of Dudley's model system (See 1.2.14).[12]

Steps (*xi)* and (*xii)* (to give **15**) were simply to change the protecting group from benzyl to SEM, prior to attachment of the side chain. Debenzylation of **14** proved troublesome, requiring the rather harsh Ca/liquid NH_3 combination, which also reduced the ketone to the alcohol. Oxidation with pyridinium dichromate regenerated the ketone, and the nitrogen was then protected with SEM.

The synthesis of the side chain, and its attachment to the core, is shown in Scheme 2



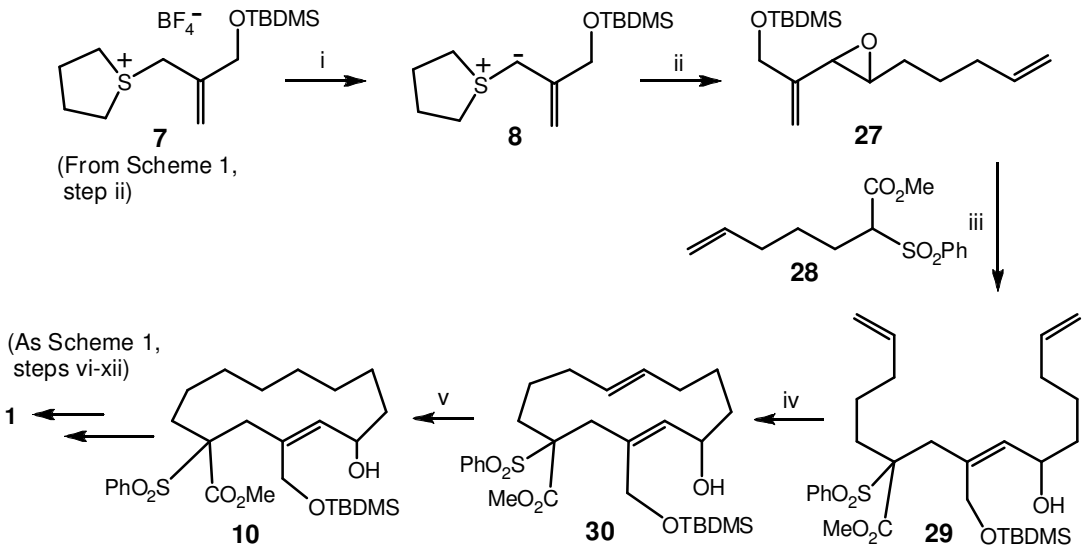
i) a) NaOH, MeOH, reflux; b) TBDMS-Cl, Imidazole, DMF; c) K_2CO_3, MeOH, THF, H_2O, 52% (3 steps) ii) $Me_2C{=}CCl(NMe_2)$, DCM yield n/d; iii) Br_2 in AcOH 90% iv) a) NaOH,H_2O b) Cu-chromite, quinoline 180°; c) TsCl, DMAP, Et_3N 52% (3 steps); v) a) BuLi -78°; b) $ZnCl_2$ -78°; c) $Pd(PPh_3)_4$ & **18,** 43-61% (3 steps); vi) PPTS, MeOH 76% vii) a) K_2CO_3/MeOH; b) KH, TIPS-Cl, 62% (2 steps), viii) a) BuLi, THF, -50°; b) $CeCl_3$, -78° (not isolated, used in solution; ix) **15,** 62% (3 steps); x) TBAF; THF xi) aq HCl, 76%

Scheme 2

Reaction of the organocerium reagent **25** with the SEM-protected core **15**, followed by removal of both silyl protecting groups with TBAF (Scheme 2, step *x*) and acid dehydration (step *xi*) gave racemic roseophilin **1**.

1.2.2 Fürstner's 2nd Synthesis (formal total, racemic) - 1999

This route[13] (shown in Scheme 3) is largely a modification of Fűrstner's first synthesis (1.2.1), but in this case the coupling between the β-sulfonyl ester and the vinyl epoxide (Scheme 1, step *v*) which previously effected macrocyclization is now an *inter*molecular step (Scheme 3, step *ii*). The open-chain product **29** was subsequently cyclized by RCM (Scheme 3, step *iv*) . The authors considered this to be a more versatile route than their previous one, in that it could readily be adapted to prepare analogues of roseophilin. Analogues of **27** could readily be prepared from **8**, and analogues of **28** could be prepared in a single step from commercially available methyl phenylsulfonyl acetate. The route is one step longer than the original version, however the overall yield was similar. It should be noted that the RCM was performed prior to the formation of *either* of the five-membered rings; the RCM reaction was not required to overcome significant strain (see 1.2.18).

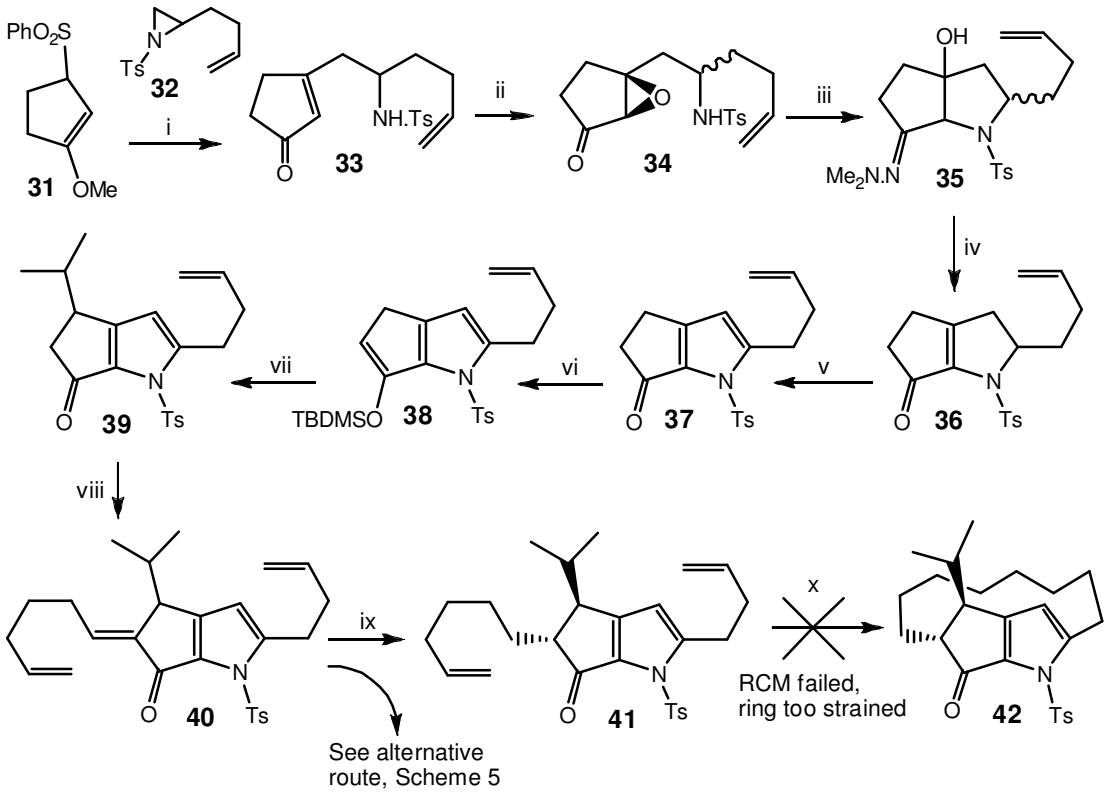


i) *t*-BuLi; ii) hex-5-enal 80%; iii) cat. $Pd(PPh_3)_4$ & **28**, 84%; iv) Grubbs Catalyst 85%
v) Wilkinsons' Catalyst, H_2, EtOH 90%

Scheme 3

1.2.3 Fuchs' Synthesis (formal total, racemic) - 1997

Fuchs, Kim and Figueroa[10] published their synthesis (Schemes 4 and 5) of the core of roseophilin in 1997, after a preliminary publication of the first six steps in 1996.[14] In this case, the central bicyclic portion was first assembled, complete with two alkene-terminated side-chains **41**, before attempting RCM (Scheme 4, step *x*). The RCM reaction failed.

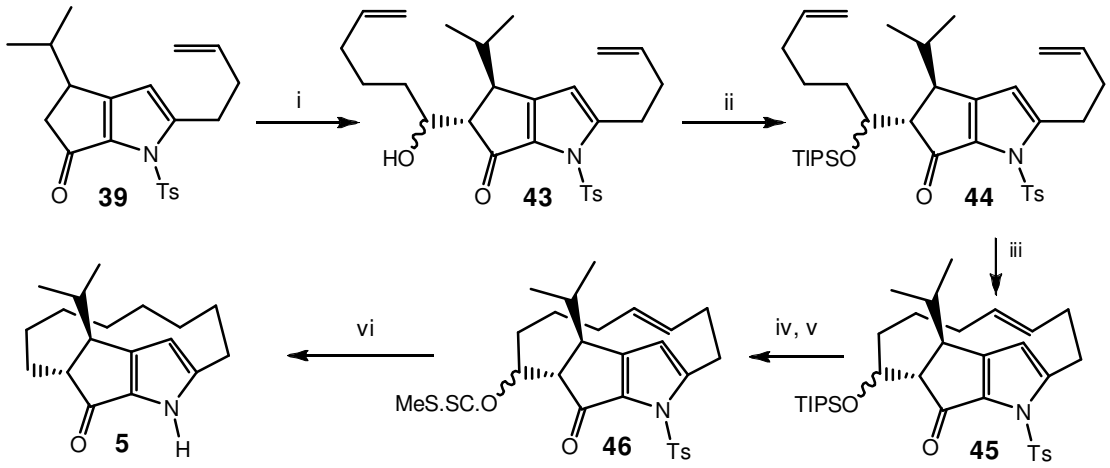


i) a) BuLi b) **32,** 95%; ii) H_2O_2, NaOH, MeOH, 74%; iii) a) 1,1-dimehylhydrazine, EtOAc, $MgSO_4$, cat. $Et.CO_2H$; b) THF,H_2O, SiO_2 78% (2 steps); iv) a) MsCl, Et_3N; b) alumina, 81% (2 steps), v) NIS, CCl_4 93%; vi) TBDMSTf, $(i\text{-}Pr)_2NEt$ 95%; vii) a) *t*-BuLi,THF; b) *i*-PrI, HMPA 74% viii) a) LiHMDS, THF; b) CH_2=CH.$(CH_2)_3$CHO; c) MsCl, Et_3N,THF; d) DBU,THF, 80%; ix) a) L-Selectride, THF (cis/trans 1:1) b) t-OBuK 94% (cis/trans 1:99) x) Grubbs' Catalyst

Scheme 4

Investigation by molecular modelling showed that, with the inclusion of a tri-isopropyl silyloxy (OTIPS) group adjacent to the bicyclic portion **44**, there existed a global-minimum energy conformation with both 'arms' in proximity, thereby favouring RCM. Accordingly the TIPS-substituted derivative **44** was synthesised, followed by successful RCM to give **45** (Scheme 5, steps *i-iii*). Hydrogenation of the (unwanted) double bond

formed by RCM, followed by removal of the O-TIPS group with HF, followed by removal of the OH, *via* the xanthate (Barton-McCombie deoxygenation)[15] gave the core **5.**



i) a) LiHMDS; b) 5-hexenal, 95%; ii) TIPSCl, $AgNO_3$,DMF 97%; iii) Grubbs' catalyst 60%; iv) a) Pd/C, EtOH, H_2; b) HF, CH_3CN, 85% (2 steps); v) a) NaH, CS_2,THF; b) MeI, 77% (2 steps); vi) Ph_3SnH, AIBN benzene, 90%

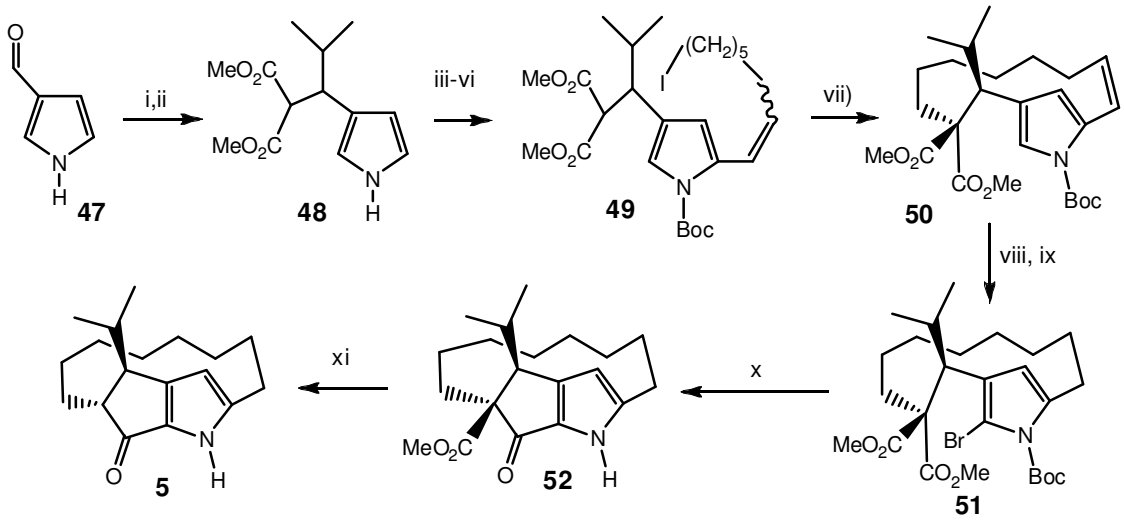
Scheme 5

It seems to have been accepted from this time that macrocyclization on systems where the fused bicyclic system is already closed requires some form of steric assistance. Such assistance may be conformational, as seen here (where a bulky side-chain substituent leads to a conformation favouring cyclization), or configurational, such as preliminary 'bending' of the bicycle (see 1.2.10) or of one of its side-chains (see 1.2.4). The idea that such assistance is *always* necessary was disproved (see 1.2.15) by Frontier and Bitar in 2008.[16]

1.2.4 Terashima's Synthesis (formal total, racemic) -1998

Terashima and co-workers published their synthesis of the core in 1998[17] following work with model compounds published in 1995.[18] In this route, neither RCM nor π–allyl palladium chemistry were utilized (Scheme 6). Macrocyclization (Scheme 6, step *vii*) was effected by an ionic nucleophilic displacement on a malonate residue in the presence of caesium carbonate. The synthesis commenced with the pyrrole portion intact **47**, but macrocylization was performed prior to closure of the cyclopentenone ring.

A notable feature of this route is that closure of the *cis/trans* mixture **49** can be effected only with the *cis* component. The macrocycle **50** was therefore obtained solely with a *cis*-olefinic bond. The *cis*-configuration presumably allows the side-chain to adopt a conformation with the iodide sufficiently close to the malonate anion to permit reaction. The issue of strain and macrocyclization once again arose, in this case even with only one half of the bicycle closed.



i) Dimethyl malonate, piperidine, pyridine, 70%; ii) *i*-PrMgBr, THF 81%; iii) a) $POCl_3$, DMF; b) AcONa, H_2O, 96%; iv) Boc_2O, DMAP, MeCN 80%; v) $TfO\text{-}(CH_2)_7P^+Ph_3Br^-$, NaHMDS, THF, 88% *cis*/*trans* 3:1; vi) a) pTSA, $CHCl_3$, MeOH; b) MsCl, DMAP, pyridine; c) NaI, acetone, 81%(3 steps) *cis*/*trans* 3:1; vii) Cs_2CO_3 DMF 38%; viii) Pd, H_2, toluene 90%; ix) a) TFA, CH_2Cl_2; b) $PyHBr.Br_2$, THF; c) Boc_2O, DMAP, CH_3CN, 63% (over 3 steps); x) *n*-BuLi THF/HMPA 38%; xi) NaCN, DMSO, H_2O 81%

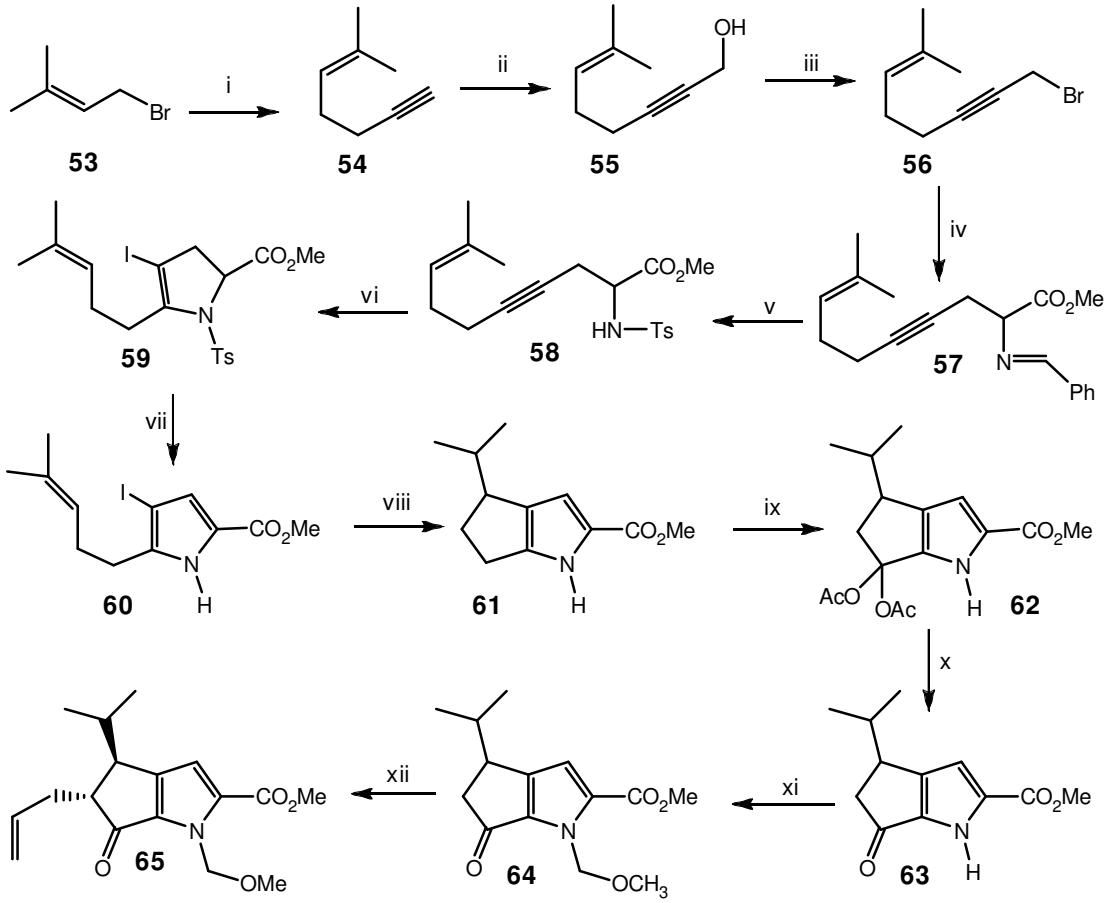
Scheme 6

Closure of the cyclopentenone ring was effected *via* the α-lithiopyrrole. In order to generate this, the BOC was first removed with TFA, followed by α-bromination of the pyrrole with $PyHBr.Br_2$, and then the pyrrole nitrogen re-protected with BOC, to give **51**

(Scheme 6, step *ix*). The α-lithiopyrrole was then generated by metal/halogen exchange with *n*-BuLi (Scheme 6, step *x*) to give **52**. The closure was completely diastereoselective, due to the steric bulk of the isopropyl group. Finally the methoxycarbonyl group was removed via a Krapcho demethoxycarbonylation[19] with solution of sodium cyanide in DMSO/water to give **5**.

1.2.5 Knight's Model Synthesis -1999

Knight and Fagan outlined a proposed route (Scheme 7) directed towards roseophilin in 1999.[20]



i) $HC{\equiv}CCH_2MgBr$, $HgCl_2$, CuCl, Et_2O*; ii) BuLi, THF, $(HCHO)_n$*; iii) NBS, PPh_3, DMF*; iv) N-benzylidene glycine methyl ester, LDA, THF, & **56***; v) a)1M HCl, Et_2O, rt; b)TsCl, Et_3N, DMAP*; vi) I_2/K_2CO_3,CH_3CN, 50%; vii) DBU/DMF 90%; viii) Bu_3SnH AIBN 60% ix) $Pb(OAc)_4$ $CHCl_3$ 95%; x) 1M HCl*; xi) MOMCl*; xii) LDA $CH_2{=}CHCH_2Br$*

* Yield not stated by authors

Scheme 7

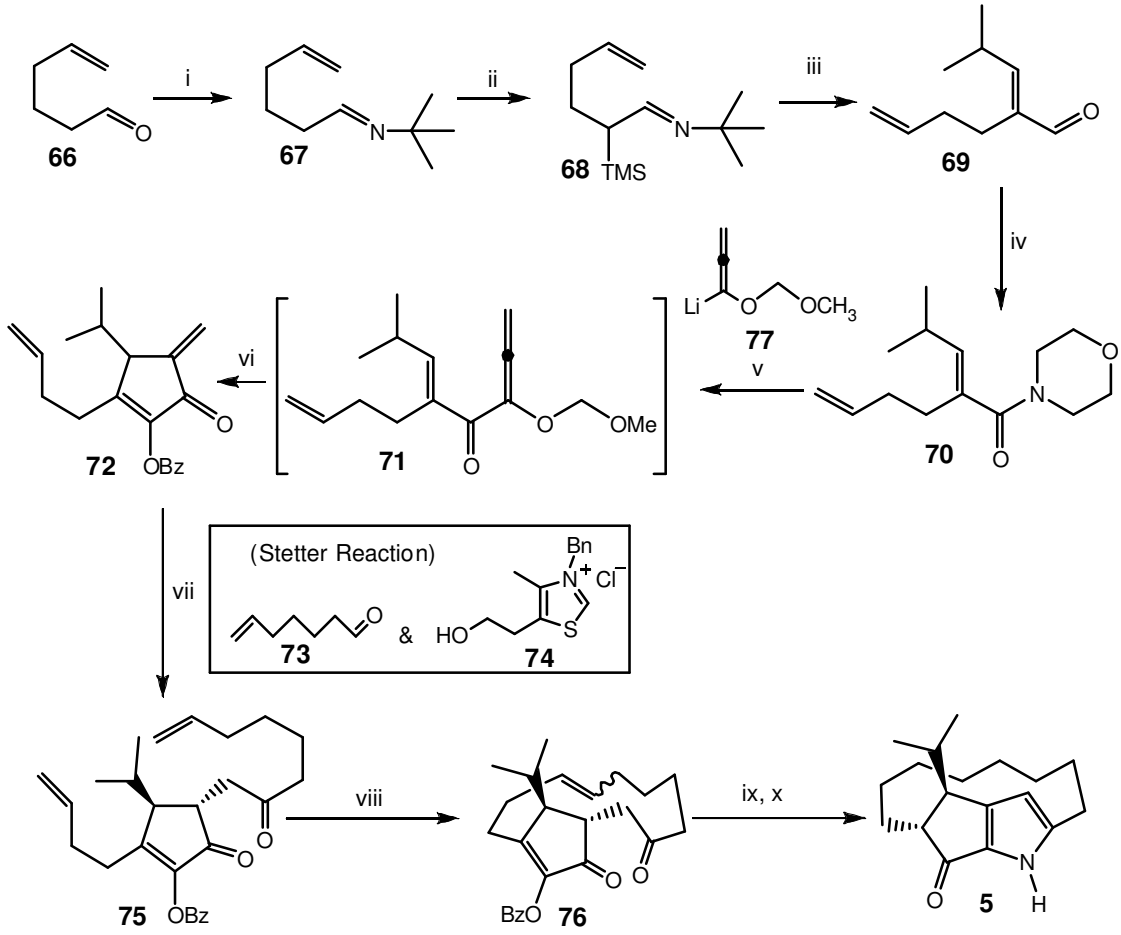
The pyrrole was neatly assembled (Scheme 7, step *vi*) from an acetylene **58** by iodination and the use of the N-tosyl protecting group for elimination (as p-toluenesulf*inate*), giving the iodopyrrole **60**. The cyclopentenone was formed by closure of the ring (with loss of iodine) using Bu_3SnH and AIBN (step viii), as a cyclo*pentane*, and then (step ix) oxidizing this with lead tetraacetate to the *gem*-diacetate **62,** which was subsequently hydrolysed to the ketone. Protection of the nitrogen as its MOM derivative, followed by α-alkylation of the ketone with allyl iodide installed an allyl side-

chain with the desired stereochemistry with respect to the isopropyl group, presumably due to the steric bulk of the latter

The radical closure of the cyclopentane ring should be noted. Later papers by these authors and Song on the α-acylation of pyrroles, and their subsequent annelation[21,22] by means of the Nazarov cyclization[23] are referenced by Frontier in her 2008 synthesis[16] (see 1.2.14). Song's own synthesis was published in 2011 (see 1.2.15.).[24]

1.2.6 Tius' 1st Synthesis (formal total, racemic) -1999

Tius and Harrington published their synthesis[25] of the core in 1999 (Scheme 8) The synthesis commenced with the construction of a branched chain containing the isopropyl moiety at one end, and an alkene (later required for RCM) at the other. The key features of this synthesis are the reaction of a lithiated allene upon an amide, the product of which undergoes a variant of the Nazarov cyclization upon acidic work-up, and the use of a Stetter reaction[26] to incorporate a terminally-unsaturated aldehyde.



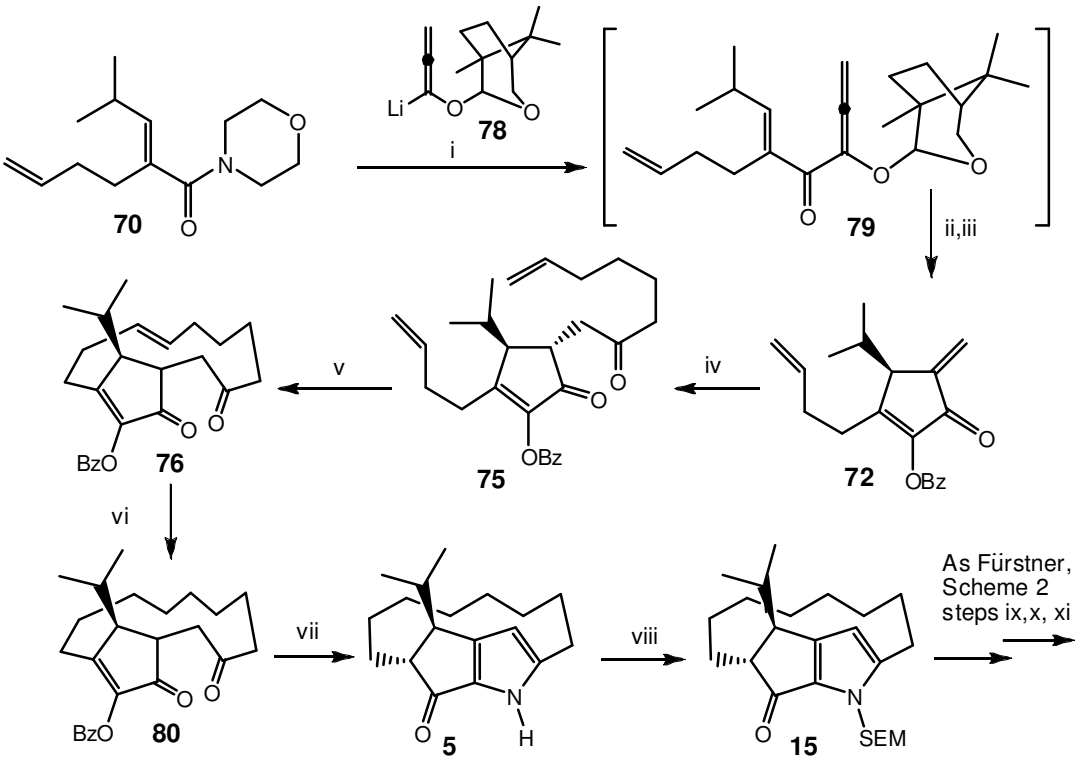
i) *t*-BuNH$_2$ 94%; ii) LDA, THF, TMSCl, -78° to 10°; iii) a) LDA, *i*-PrCHO -78° to 10°; b) oxalic acid, H$_2$O, 71% (3 steps); iv) a) NaClO$_2$ 2-methyl-2-butene; b) CBr$_4$,morpholine, PPh$_3$, 81% (2 steps); v) a) **77,** THF, -78°; b) AcOH vi) Bz$_2$O, Et$_3$N, 49% (2 steps); vii) **73**, **74**, dioxane, 60%; viii) Grubbs' catalyst, DCM 40° 90% ix) Pd/C, H$_2$,THF 92% x) (NH$_4$)$_2$CO$_3$, EtCO$_2$H, 140°, 52%

Scheme 8

This terminal double bond thereby became the remote end of the side chain of **75**, which was subsequently closed by RCM, *prior* to the closure of the pyrrole ring. The authors explicitly stated that this order was chosen in the light of Fuchs' earlier observations on RCM and the effect of strain.

1.2.7 Tius' 2nd Synthesis (Total, chiral) - 2000

In 2000 Tius published an asymmetric cyclopentannelation where the MOM group of the lithioallene **77** was replaced with a chiral substituent to give the chiral lithioallene **78**.[27] This was used in conjunction with a modified work-up in hexafluoroisopropanol (HFIP) which stabilizes carbocations. This chiral auxiliary is 'traceless', in that it is lost in the work-up. This allowed both enantiomers of **72** to be prepared in be prepared in high *ee*.



i) Chiral lithio-allene **78**, 30%; ii) HCl/HFIP/TFE -78° 78% 86% *ee* iii) Bz_2O, Et_3N, DMAP 49%
iv) **73**, **74**, dioxane, 77% v) Grubbs Catalyst, DCM 40° 91%; vi) Pd/C, H_2, THF recryst 87% 99% *ee*
. vii) $(NH_4)_2CO_3$, $Ti(O\text{-}i\text{-}Pr)_4$, 54%, viii) KH, SEMCl, DMF rt

Scheme 9

Tius then applied this methodology to his existing roseophilin synthesis (Scheme 9, steps i,ii), and, in 2001 published a second synthesis, total and chiral, of roseophilin.[28] The work-up following reaction of the chiral lithioallene was done at –78°C with a solution of HFIP and 1,1,1-trifluoroethanol with HCl, the mixture being necessary as HFIP freezes at –4°C. Recrystallization of **80** gave substantially enantiomerically pure material, which was subsequently converted (steps vii, vii) to the SEM-protected core **15** used by Fürstner (see 1.2.1, Scheme 2).

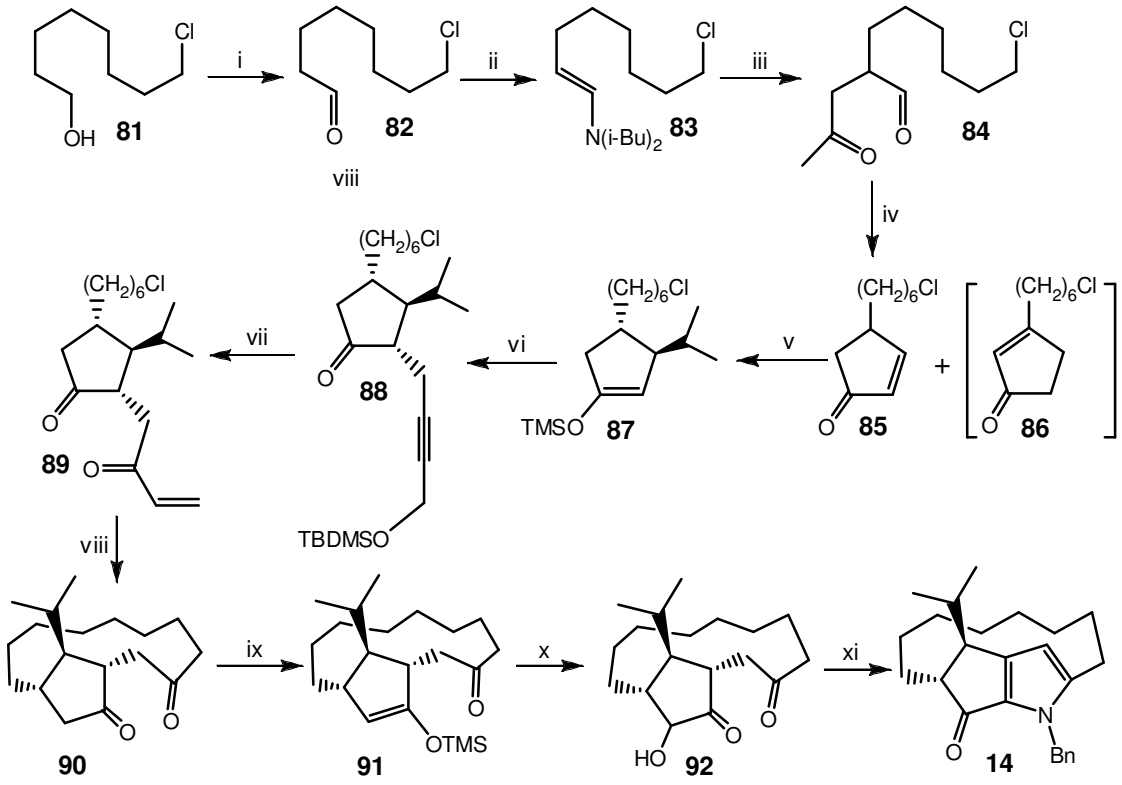
The publication of this total synthesis coincided with that of Boger[2] (see 1.2.11). The publications were placed (intentionally & diplomatically) adjacent in the same issue of Journal of the American Chemical Society, and each acknowledges the courtesy of the other in sharing their results.

Tius produced (22*R*,23*R*)-roseophilin identical with the natural material, thus definitively proving the absolute stereochemistry which had been unknown until this point. Boger produced the opposite enantiomer. The absolute stereochemistry was therefore inarguably proven by two independent, unambiguous routes, one to each enantiomer.

Both Tius and Boger reported difficulty in repeating Fűrstner's cerium-mediated coupling of the side-chain. It appears that this coupling is very sensitive to reaction conditions.

1.2.8 Robertson's Synthesis (formal total, racemic) – 1999-2000

Robertson and Hatley published their synthesis of the core (see Scheme 10) in a communication in 1999,[29] which was followed up with a full paper[30] in 2000.



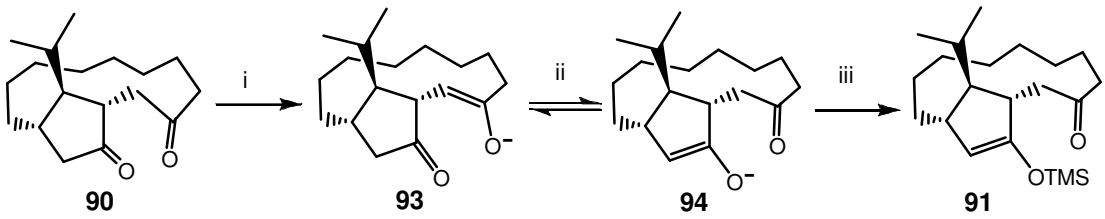
i) Swern 98%; ii) *i*-Bu_2NH, K_2CO_3, rt; iii) chloroacetone, NaI, 18-crown-6, THF, 58% (2 steps)
iv) NaOH, Et_2O, rt 86%; v) *i*-PrMgCl, LiI,TMSCl, THF, -78° 96%; vi) a) MeLi, DMPU, THF
b)TBDMSO-$CH_2C{\equiv}CCH_2I$, -78° 62%; vii) a) H_2SiF_6, CH_3CN 96%; b) $Hg(OAc)_2$, AcOH, HCl, 48%
viii) a) NaI, MEK, 89%; b) Bu_3SnH, AIBN, benzene 45%; ix) LDA, THF, -30° TMSCl (equilibrate)
x) a) Dimethyldioxirane DCM (46% 2 steps); b) Aq H_2SiF_6 83% (2 steps); xi) $BnNH_2$, AcOH, MeOH (air oxidation) 25%

Scheme 10

The cyclopentenone portion was assembled in the form of an αβ-unsaturated cyclopentenone **85** with an n-hexyl side chain terminated by a chlorine. The cyclization (Scheme 10, step *iv*) gave inconsistent yields. Relative stereochemistry was introduced by conjugate addition of *i*-PrMgCl to **85** mediated with cuprous iodide and lithium chloride. *Anti*-addition was favoured due to the bulk of the chlorohexyl and the incoming isopropyl. Similarly, alkylation with the propargylic iodide, following α-deprotonation of **87**, (Scheme 10, step *vi*), proceeded *anti* to the isopropyl.

Desilylation and acetoxymercuration of the acetylenic portion of **88** converted this into an αβ-unsaturated ketone **89**. Exchange of the chlorine for iodine using Finkelstein conditions[31] was followed by radical macrocyclization with AIBN and Bu_3SnH (Scheme 10, step *viii*).

The deprotonation and mono-silylation (Scheme 10, step ix) was unsatisfactory, as there are two carbonyls, either of which can be deprotonated (see Scheme 11).



90 **93** **94** **91**

i) LDA, THF, -78° gives **93:94** in 3:1 ratio ii) Equilibration at 0° gives mainly **94** iii) TMSCl

Scheme 11

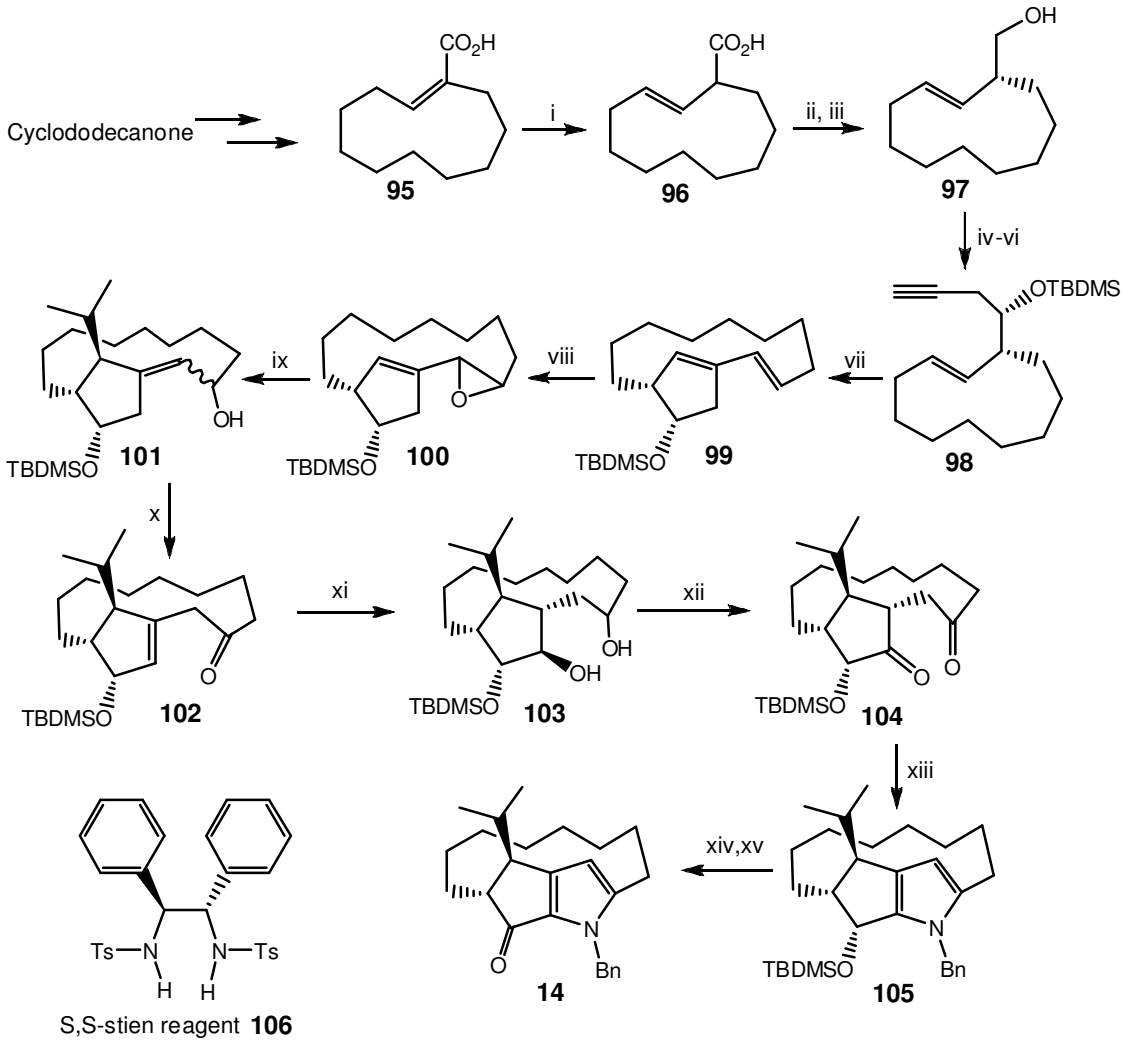
The kinetic enolate **93** is not the desired one. Permitting the reaction to equilbrate at 0° gave a mixture in which the desired enolate **94** predominated, which was subsequently silylated to give the desired silyl enol ether **91**.

Oxidation with dimethyl dioxirane, desilylation and ring-closure of the pyrrole with benzylamine in acetic acid gave the ketone **14** rather the expected alcohol. Presumably, air was not sufficiently excluded, and oxidation of the alcohol occurred.

Unfortunately, the synthetic value of this route is greatly reduced by poor yields.

1.2.9 Trost's Synthesis (formal total, chiral) - 2000

Trost and Doherty's asymmetric synthesis of the core[32] is shown in Scheme 12 below.



i) a) BuLi,HMPA (to dianion), b) aq $NaHSO_4$, 87%; ii) DCC, DCM, (-)menthol, DMAP 83%; iii) $LiAlH_4$, Et_2O, 94%; iv) Dess Martin periodinane 77%; v) BBr_3 HC $\equiv CH_2SnPh_3$, SS-stien reagent **106**, DCM 80%, vi) TBDMSCl, imidazole, DMAP 67%, vii) $PtCl_2$, toluene 98% viii) a) NBS, THF, H_2O b) NaOH ix) *i*-PrMgBr,CuBr,THF, 62% (2 steps); x) a) TPAP,NMMO, 87%; b) DBU, CH_3CN, 75° 68%; xi) a) $BH_3.SMe_2$,Et_2O b) NaOH, H_2O_2 89%; xii) TPAP, NMMO, 4Å sieve,DCM 93% xiii) $BnNH_2$, MeOH, AcOH 60%; xiv) TBAF 87%; xv) MnO_2 79%

Scheme 12

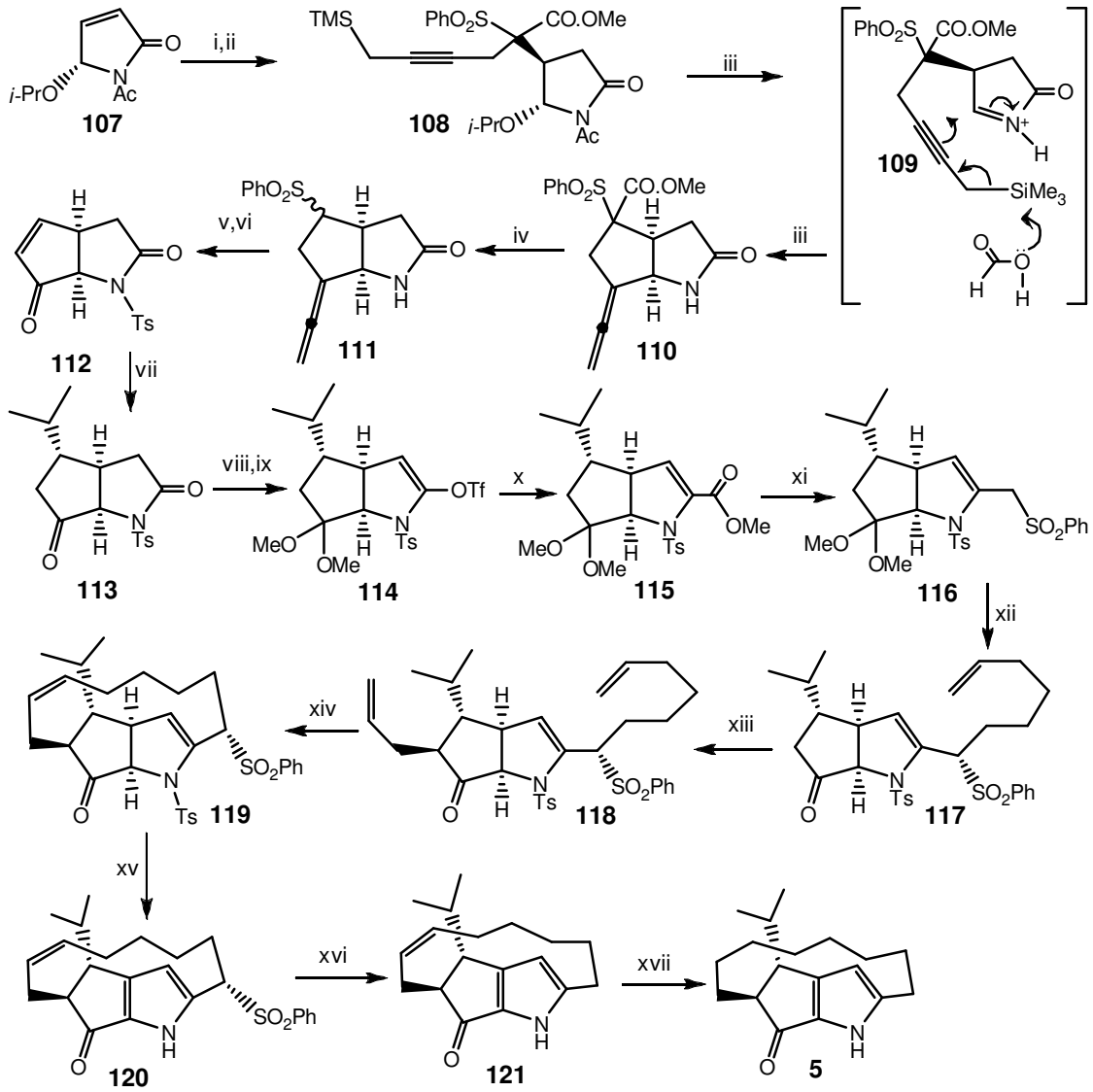
The ultimate starting material for this synthesis was actually cyclododecanone, which gives **95** when subjected to a Favorskii-type ring contraction.[33] The strategy relied upon the careful construction of the chiral substrate **98** for the metathesis (step vii).

The metathesis gave the cyclopentene **99,** establishing the carbon skeletons of both the macrocycle the cyclopentenone ring.

Chirality was introduced by esterifying acid **96** with (-)menthol (using DCC, *via* the ketene), then reducing the menthyl ester to the chiral alcohol **97** with $LiAlH_4$. This was subsequently oxidized to the aldehyde with Dess Martin periodinane. This use of menthol as a 'traceless' auxiliary is particularly attractive, as both enantiomers of menthol are readily available and inexpensive, making the route equally amenable to the synthesis of either enantiomer of the final product. The second stereocentre was diasteroselectively constructed from this aldehyde using an allenylborane derived from the chiral stilbene-diamine-derived '(*S,S*)-stien' reagent **106**, boron tribromide, and propargyl triphenylstannane.[34] This diastereoselective propargylation, and the innovative use of the subsequent metathesis may be regarded as the key features of this synthesis.

1.2.10 Hiemstra's Synthesis (formal total, chiral) – 1998 & 2000

Hiemstra's group published this synthesis (Scheme 13), in 2000,[11] following a preliminary publication in 1998.[35]



i) $MeCO_2CH_2SO_2Ph$, Et_3N, DMF, 100%; ii) a) NaH,DMF,rt b) TMS-$CH_2C{\equiv}CCH_2I$, 80%; iii) a) Me_2NH, DCM b) HCOOH 80%; iv) a) LiOH, THF,H_2O b) Pyridine 90° 80% v) a) *n*-BuLi b) TsCl 65%; vi) a) O_3, b) DMS c) Al_2O_3 62% vii) CuI, $BF_3.OEt_2$, *i*-PrMgCl, 83%; viii) $HC(OMe)_3$, MeOH, pTSA 98%; ix) a) KHMDS, HMPA b) Comin's Reagent x) $Pd_2(dba)_3$, $AsPh_3$, CO, 20 bar, LiCl, MeCN 71% (2 steps) xi) a) DIBAL, 71% b) PPh_3, imidazole,I_2,MeCN 96%; c) $PhSO_2Na$, 95%; xii) a) *n*-BuLi, HMPA b) 1-bromohex-5-ene, 65%; c) HCl, acetone, 60°, 99%; xiii) PtO_2/H_2 EtOAc 99% xiv) Grubbs' cat, DCM, 40°, 91% xv) NaHMDS, THF, 71%; xvi) Na/Hg Na_2HPO_4,THF, MeOH, 0° 94% xvii) PtO_2/H_2 EtOAc 99%

Scheme 13

The starting material for this chiral synthesis was the chiral αβ-unsaturated lactam **107**, the synthesis of which (starting from (*S*)-malic acid) was published by the same group in 1992.[36] The anion of methyl phenylsulfonyl acetate underwent a Michael-type

addition to the alkene of the lactam **107**. The addition was exclusively *trans* to the bulky *iso*-propoxy group. A second alkylation, with NaH and TMS-$CH_2C\equiv CCH_2I$ was then performed upon the activated methine of the compound to give **108**. Removal of the N-acetyl protecting group with Et_2NH, followed by treatment with formic acid generated the acylium ion **109**, removed the trimethylsilyl group and allowed cyclization to the bicyclic amide **110**. It should be noted that the central bond of the bicyclic system was saturated, and therefore the bicyclic portion was *not* planar. This had a number of important consequences.

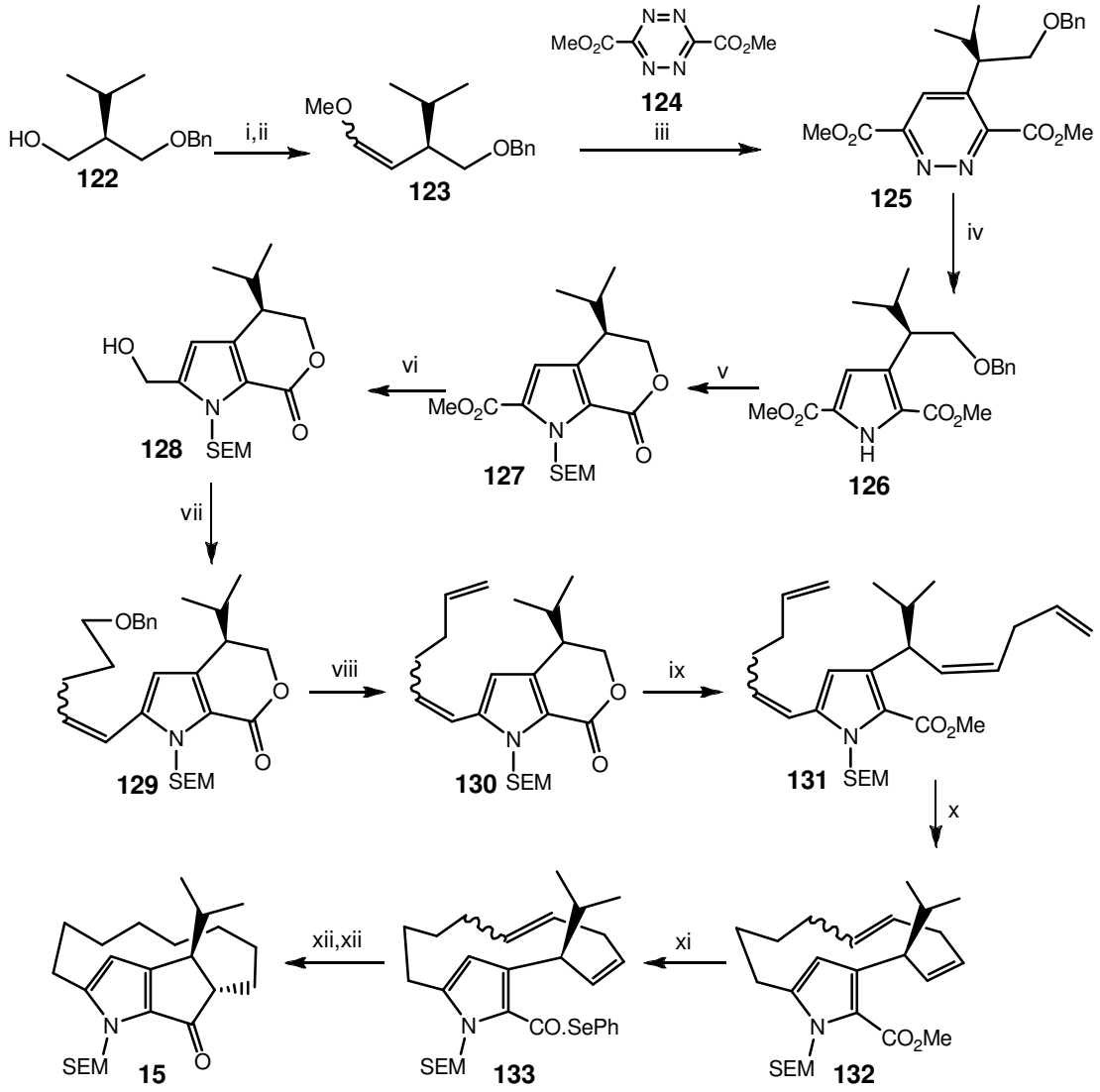
The unwanted CO_2Me group was then removed (Scheme 13, step *iv*), the nitrogen protected with Ts (step *v*), the allenyl function removed with ozone, and $PhSO_2H$ eliminated to give αβ-unsaturated ketone **112**. The addition of the isopropyl group (as a magnesium cuprate in the presence of BF_3) to **112** occurred *solely* on the least-hindered side of the molecule to give **113** as a single isomer.

The side chains (with the terminal double bonds needed for RCM) were installed next (Scheme 13, steps *vi–xiii*) to give **118.** The macrocycle was closed (*xiv*) under normal Grubbs' conditions to give **119**. The necessary assistance in overcoming strain (thereby permitting RCM) came from two sources. Firstly, c*onformational* assistance was provided by the bulk of the $PhSO_2$ group, which should be compared with the use of OTIPS in Fuchs synthesis (see 1.2.3). Secondly, as the bicyclic portion is bent (due to saturation of the central bond, as stated above), *configurational* assistance was also present. The net result was that the ends of the side-arms could be brought into sufficiently close proximity for metathesis to occur.

Elimination (Scheme 13, step *xv*) of the tosyl from **119** (as p-toluene*sulfinate*) gave **120**. This elimination rendered the central bond of the bicyclic portion unsaturated, thereby making it planar. $PhSO_2$ was removed from **120** by sodium amalgam (step *xvi*), giving **121.** Finally, the unwanted double bond, introduced by the metathesis, was removed by hydrogenation (step *xvii*) over platinum oxide to give the core **5.**

1.2.11 Boger's Synthesis (total synthesis, chiral) - 2001

Boger and Hong's chiral total synthesis[2] (Scheme 14) was published simultaneously with Tius's (1.2.7) and (unlike Tius's) produced the unnatural enantiomer of roseophilin.



i) TPAP, NMMO, 4Å sieve, DCM 100%; ii) $MeOCH{=}PPh_3$, THF, iii) $CHCl_3$, **124**, 91% (2 steps); iv) Zn, TFA, 52%; v) a) Pd/C, H_2, MeOH; b) CSA, benzene, 77% (2 steps); c) THF, NaH, SEMCl 92%; vi) a) LiI DMF,130° 74% b) Cl.CO.OEt, Et_3N, THF; c) $NaBH_4$ 90% (2 steps); vii) a) MnO_2,DCM; b) $BnO(CH_2)_4P^+Ph_3Br^-$, THF, -78°, NaHMDS, 96% (2 steps); viii) a) Pd/C, H_2, MeOH; b) TPAP,NMMO, 4Å sieve, DCM c) CH_3-$P^+Ph_3Br^-$, NaHMDS, THF, 67% (2 Steps); ix) a) LiOH, THF, MeOH, H_2O; b) MeOH,toluene, $TMSCHN_2$; c) TPAP,NMMO, DCM, 4Å sieve; d) THF, $CH_2{=}CH(CH_2)_2P^+Ph_3Br^-$,NaHMDS, 91% (4 steps); x) Grubbs' catalyst DCM 40° 72%; xi) a) NaOH, EtOH, H_2O; b) THF, Et_3N, $Cl.PO(OEt)_2$, PhSeNa 83% (2 steps); xii) benzene, Bu_3SnH, AIBN, 75%; xiii) EtOAc, PtO_2 H_2 100%

Scheme 14

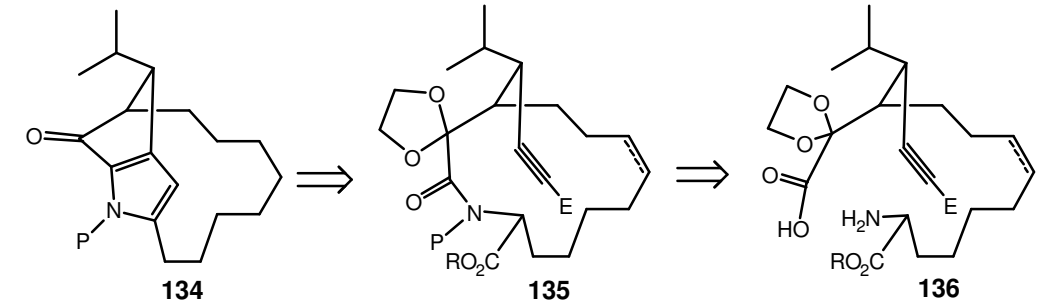
Considering that the absolute stereochemistry had not been determined until this time, there was only a 50% chance of obtaining the desired natural enantiomer. Fortunately,

any disappointment Boger may have felt was no doubt alleviated by this isomer being both previously unknown, and also turning out to be more active in *in vitro* cytotoxicity tests than the natural enantiomer.[2]

The synthesis commenced from the chiral alcohol **122**, which was converted (Scheme 14, steps i,ii) by oxidation and Wittig chemistry to an optically active enol ether **123**. This was then subjected to an inverse-electron-demand Diels-Alder reaction (a speciality of Boger's[37]) with the 1,2,4,5 tetrazine **124** to give the diazine **125**. This was converted (step *iv*) to the pyrrole **126** with Zn/TFA *via* reduction to the *bis*-imine/enamine, and cyclization with the loss of ammonia. Removal of the benzyl with Pd/H_2 to give the alcohol (step *v) a*) was followed by lactonization (step *v) b*), thereby differentiating the two methoxycarbonyl groups of **126**. The nitrogen was then protected with SEM (step *v)* c), to give **127**. The remaining CO_2Me was then elaborated (steps *vi-viii*) to give **130,** which has the side-chain with a terminal methylene required for metathesis . Hydrolysis of the lactone, esterification with $TMSCHN_2$, and elaboration of the unmasked alcohol facilitated installation of the second side-chain, giving **131**. The macrocycle was closed by the usual metathesis to give the pyrrole-containing macrocycle **132**. The incipient cyclopentenone-ring was still open at this stage, so ring strain was not a barrier to RCM. Conversion of **132** to the phenyl selenoester **133**, followed by radical cyclization and hydrogenation gave the SEM-protected core **15**. The cerium-mediated coupling of Fürstner as modified by Tius was used to attach the side chain and complete the synthesis.

1.2.12 Dyke's Proposed Synthesis (models) - 2004

Dyke and Bryson[38] published a preliminary paper in 2004, outlining a possible synthetic strategy towards roseophilin (Scheme 15).

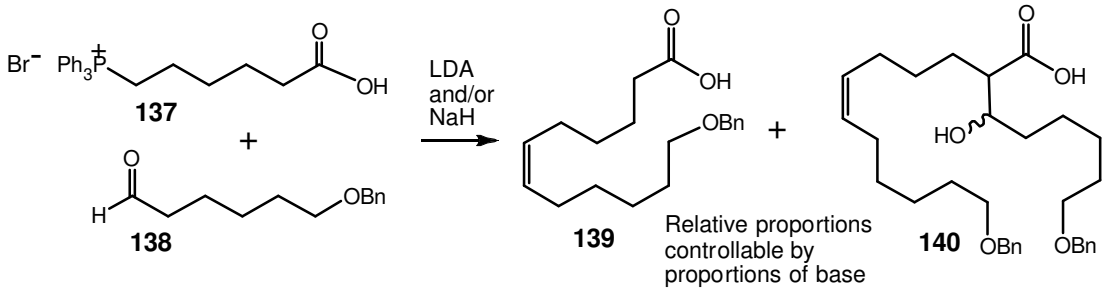


134 **135** **136**

P = Protecting Group

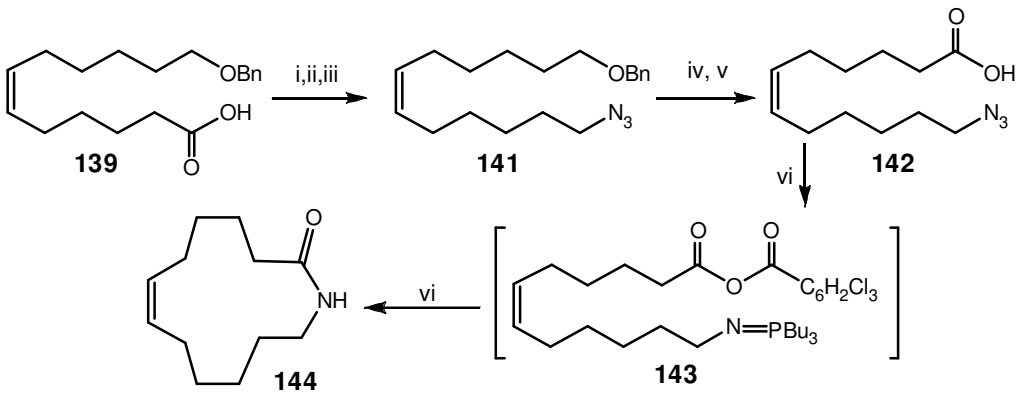
Scheme 15

Preparation of the substrate for macrocyclization required methodology for the construction of long-chain α-substituted carboxylic acids and the authors demonstrated how a Wittig reaction intended to prepare **139** could be accompanied by an aldol-type condensation to give **140**, and how the relative proportions of **139** and **140** could be controlled by varying the base (NaH/LDA) and the stoichiometry (Scheme 16).



Scheme 16

They also demonstrated that the method of Vilarassa for macrolactamization,[39] where a mixed anhydride and DMAP act upon a phosphazene formed *in situ* from tributylphosphine and an azide, is applicable to the synthesis of a 13 membered lactam **144** (Scheme 17, overleaf).



i) $LiAlH_4$ 36%; ii) PPh_3, I_2, imidazole 96%; iii) NaN_3 58%; iv) BCl_3 94% v) Jones' Reagent 95%
vi) a) $Cl.CO.C_6H_2Cl_3$,Et_3N b) PBu_3,DMAP 56%

Scheme 17

This 13-membered lactamization may be regarded as a model for a synthesis of roseophilin. This would be unusual in that an initial macrocyclization would be *via* the lactam, *i.e.* the red/blue route in Figure 3.

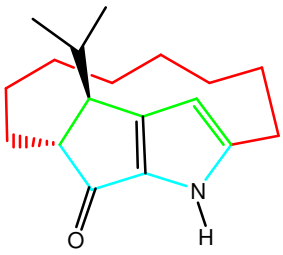
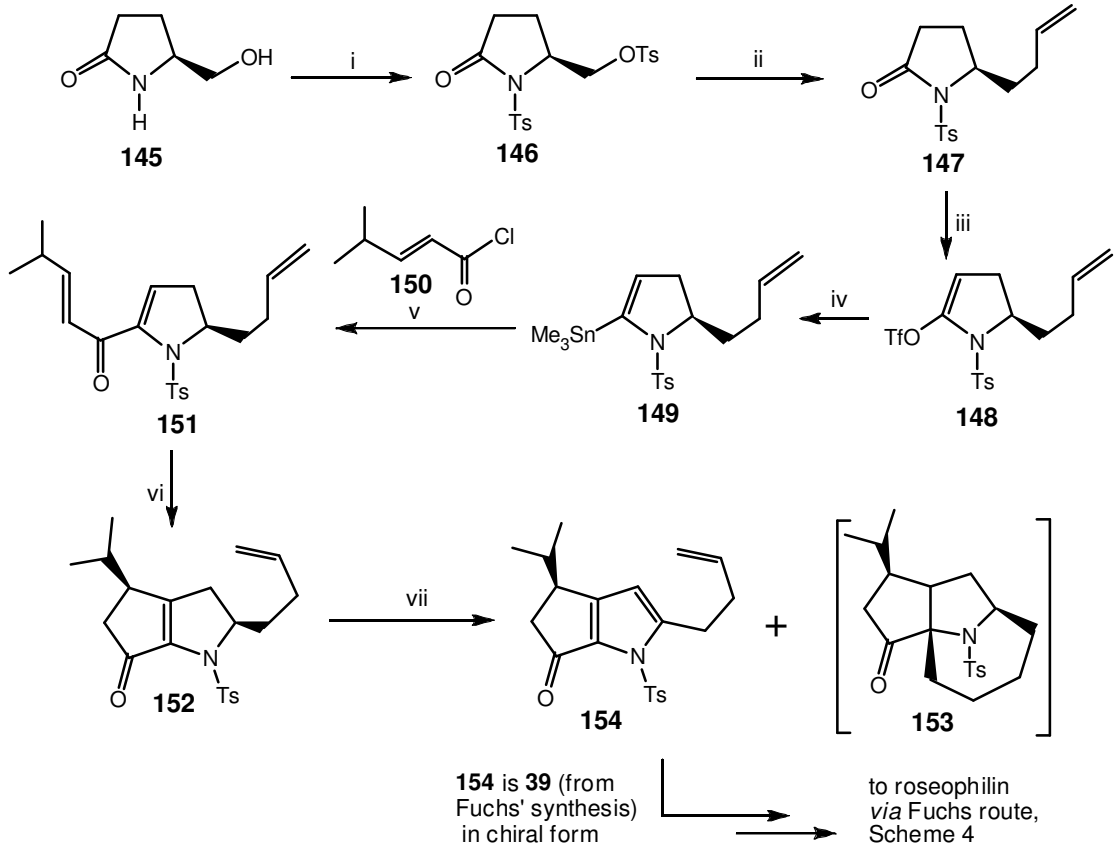


Figure 3

In the three other syntheses where the 13-membered macrocycle was closed first (*i.e.* both of Fürstner's syntheses (1.2.1, 1.2.2) and that of Trost (1.2.9)) the red/green route was taken, and the initial macrocycle was therefore carbocyclic. Despite this, and whilst the work described in this publication may be regarded as a model for a synthesis of roseophilin based upon this approach, these authors do not appear to have published any further work in this field.

1.2.13 Occhiato's Synthesis (formal total, chiral) - 2005

The Occhiato group's synthesis[40] of 2005 is shown in Scheme 18. It provides an alternative route to the chiral intermediate **154** which appeared in *racemic* form as **39** in Fuchs' route (see 1.2.3, Scheme 4). As such, this work constitutes a formal total synthesis in its own right, as well as increasing the utility of Fuchs' route.



i) TsCl, Et_3N, DMAP,DCM; ii) a) CH_2=$CHCH_2MgCl$,THF; b) TsCl, LiHMDS,THF, 56% (3 steps); iii) $PhNTf_2$, KHMDS, THF; iv) Me_6Sn_2, $Pd(MeCN)_2Cl_2$, Ph_3As, THF,**150;** v) $Pd(Ph_3)_4$, toluene, reflux, 24% (3 steps); vi) TFA 43% vii) DDQ 48%

Scheme 18

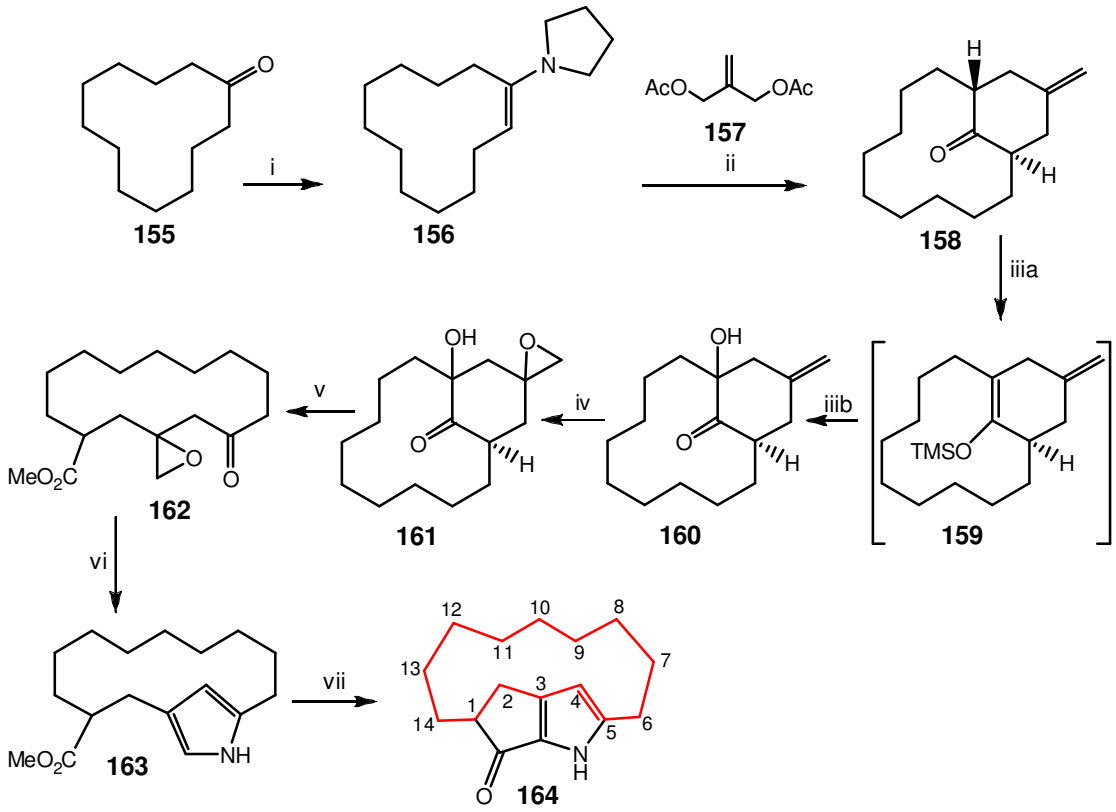
The construction of the Nazarov precursor **151** is noteworthy. Whilst the (*E*)-4-methyl-2-pentenoyl moiety was efficiently introduced in one piece using the acid chloride **150**, the Stille coupling[41] utilized (Scheme 18, steps *iii*-*v*) was unsatisfactory, not only with regard to yield (24% over 3 steps), but it also required the use of the highly toxic reagents hexamethylditin and triphenylarsine.[42]

The Nazarov reaction (Scheme 18, step *vi*) to **152** proceeded in moderate yield (47%), although a by-product which appeared to be the tricycle **153** was also isolated. Despite

this the desired compound, **152** was formed as a single isomer, and chirality was retained. Oxidation of **152** to **154** with DDQ completed the formal total synthesis.

1.2.14 Dudley's Model Synthesis -2005

In 2005 Dudley and Salamone published[12] an elegant and unusual synthesis of a model compound **164** closely related to the core of roseophilin (Scheme 19). In this compound the *ansa*-bridge is one carbon longer than in roseophilin, giving a total of 14 carbons in the macrocycle, shown highlighted in red in Scheme 19. This is due to the starting material chosen, cyclododecanone **155**, which was selected due to its comparative cheapness with respect to cycloundecanone. The compound **164** also lacks the isopropyl on the cyclopentenone ring.



i) Pyrrolidine, BSA, MeI (cat.); ii) **157**, $Pd(OAc)_2$,PPh_3, CH_3CN; iii) a) HMPA,LDA,TMSCl b) mCPBA,DCM c) TBAF, THF, 50% (4 steps); iv) a) mCPBA 80%; v) $Pb(OAc)_4$, MeOH, 94%; vi) NH_4OAc, CSA, MeOH, 93%; vii) a) KOH, MeOH; b) $(COCl)_2$ 77% (2 steps)

Scheme 19

The synthesis began with the conversion of **155** to enamine **156**, bridging this using a bis-allylation procedure[43] (which gave a single isomer), followed by conversion of this to the silyl enol ether. Curiously, enolization with LDA (prior to silylation) was sluggish, but proceeded efficiently in the presence of HMPA. The authors hypothesize that this may be due to the breaking up the co-ordination of lithium ion in the transition state This should be compared with the function of HMPA or DMPU in the Ireland-Claisen

rearrangement (see 2.2.1). The silyl enol ether was oxidized with mCPBA (Scheme 19, step *ii, b*), then the TMS removed with TBAF to give the hydroxyketone **160**. A further epoxidation (step *iv*) gave **161**, which was cleaved (step *v*) with lead tetra acetate to give **162**. The molecule **162** has the desired 14-membered macrocycle, the β-epoxy ketone and methoxycarbonyl functions all in position for the subsequent cyclizations. The pyrrole was closed first (step *vi*) with ammonium carbonate, then the ester hydrolysed (step *vii*, a) and closure effected (step *vii*) with neat oxalyl chloride. The latter reaction was unintended, as the acid chloride had actually been expected. It should be remembered, however, that less strain has to be overcome in this system than in that of roseophilin. The acylation requirements should perhaps better be compared to the relatively mild conditions (trifluoroacetic anhydride) required for *inter*molecular α-acylation of pyrroles,[21] later used in the syntheses of Frontier[16] (1.2.15, Scheme 20, step ii), and Song[24] (1.2.16, Scheme 23, step *v*), rather than to the harsh conditions ($SnCl_4$) for the equivalent closure (Scheme 1, step *ix*) used by Fűrstner. In this case, acylation to **164** rather than simple formation of the acid chloride is therefore, perhaps, unsurprising.

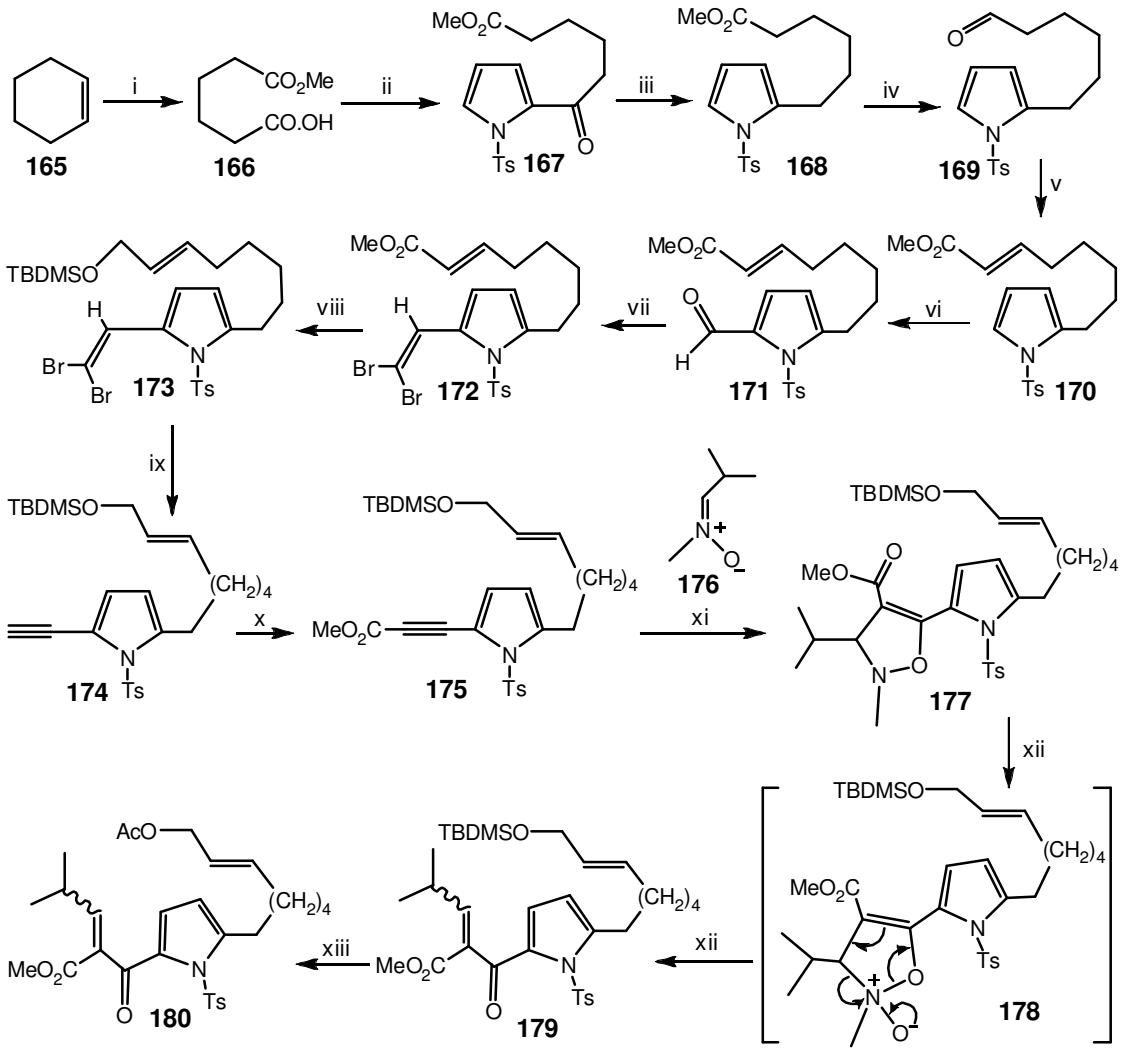
The final compound **164** was unfortunately unstable, which required characterization to be performed on the crude material.

As a synthesis in its own right, this study is impressive. As a model for roseophilin, the 'spoilers' are the absence of the isopropyl group, and that it has only been shown to work on a 14-membered macrocycle, less strained than the 13-membered roseophilin system. In fairness, Fűrstner's synthesis showed that the isopropyl could be added with all three rings closed, so this does not unduly detract from the value of the model.

The question of whether this approach would be valid in the case of the more-strained roseophilin system remains open. The fact that such a synthesis has *not* been published in the eight years that have elapsed since publication of this model strongly suggests that it has probably been tried, but without success.

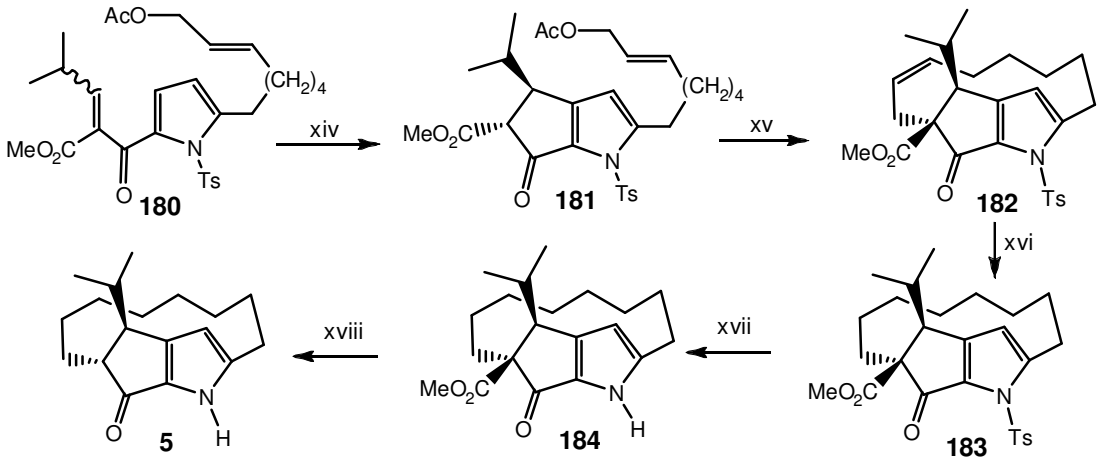
1.2.15 Frontier's Synthesis (formal total, racemic) - 2008

Frontier and Bitar's synthesis[16] is shown in Schemes 20 and 21, and has a number of interesting and significant features, particularly the use of the Nazarov reaction for closure of the cyclopentenone ring, and the macrocylization method.



i) a) O_3, MeOH,DCM; b) Ac_2O, Et_3N 72% (2 steps) c) H_2CrO_4, acetone 86%; ii) N-tosylpyrrole,TFAA, 93% iii) ZnI_2, $NaBH_3CN$, DCE, 79% iv) a) DIBAL 97%; b) Swern 92%; v) $(EtO)_2PO.CH_2COOMe$, NaH, 92%; vi) $POCl_3$, DMF, 92%; vii) CBr_4,PPh_3 DCM 95%; viii) a) DIBAL, DCM 95%; b) TBDMSCl, imidazole, 63% ix) EtMgBr 80%; x) LiHMDS, MeO.CO.Cl; xi) **176**, 80% (2 steps); xii) mCPBA DCM 92%; xiii) a) HCl, MeOH 79% b) Ac_2O, Et_3N, 92%

Scheme 20



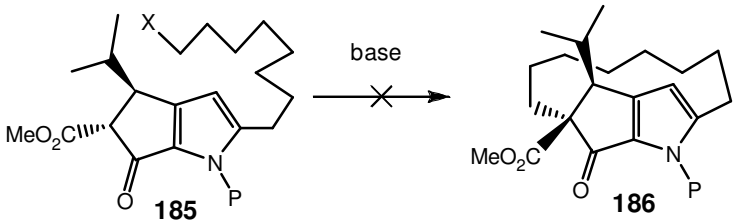
xiv) $Sc(OTf)_3$, $LiClO_4$, DCE, 79%; xv) Pd $(OAc)_2$ DPPP, 73%; xvi) Pd/C, H_2 83%; xvii) K_2CO_3, MeOH; xviii) NaCN, DMSO, 62%

Scheme 21

The synthesis started from cyclohexene **165** which was converted (Scheme 20, step *i*) to the monomethyl ester of hexane-1,6-dioic acid **166**. This was used to α-acylate N-tosylpyrrole in the presence of TFAA (Scheme 20, step *ii*) to give **167**, and then further elaborated (Scheme 20, steps *iii-xiii*) to produce the Nazarov substrate **180**.

The Nazarov reaction (Scheme 21, step *xiv*) was performed using scandium (III) triflate and lithium perchlorate in dichloroethane, mild Lewis acid conditions previously developed by Frontier.[44] A single isomer of **181** was obtained, with the isopropyl and carbomethoxy groups *trans* to each other, a characteristic of these reactions previously noted[44] by Frontier.

Given that **181** is a β-diketone, nucleophilic macrocyclization of substrates of the generic structure **185** with weak base (no further details given) was attempted, but without success (Scheme 22).



X = Leaving Group P= Protecting Group

Scheme 22

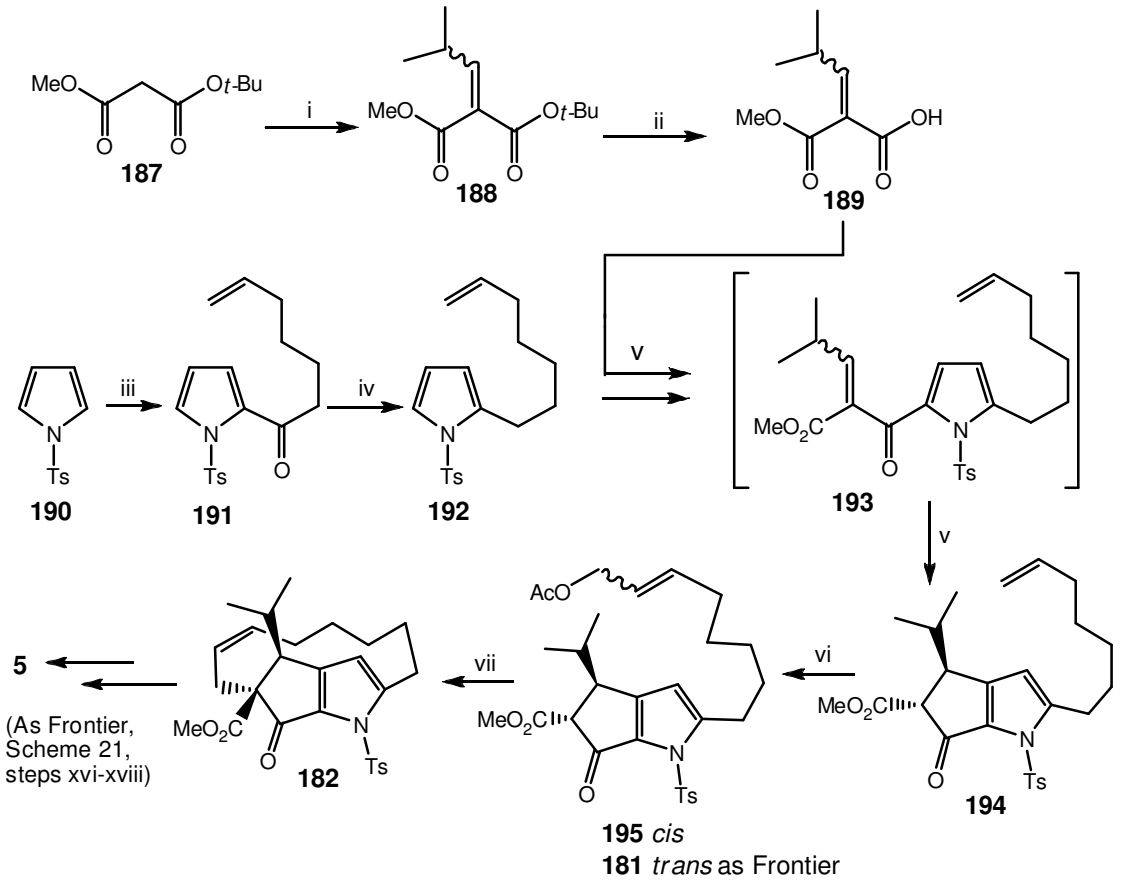
The authors observed that **185** lacked the bulky substituents on the side-chains that had been regarded, since the work of Fuchs (see 1.2.3), as being necessary to provide conformational assistance to ring closure, and were presumably unsurprised by the failure to cyclize. The actual closure was instead successfully performed (Scheme 21, step *xv*) using a π-allyl palladium species in an intramolecular Tsuji-Trost[45] reaction using a Pd(0) catalyst. Hydrogenation, removal of the N-tosyl protecting group and Krapcho demethoxycarbonylation (as in 1.2.4) completed synthesis of the core.

The publication of this synthesis dispelled the view that conformational or configurational assistance is absolutely necessary for closing the macrocycle with the bicycle fully assembled and planar. It would appear that this view *is* valid for RCM, as shown by Fuchs. It would also appear to be valid for conventional nucleophilic closure using β-diketonate anions (see Scheme 22), and is still valid with the cyclopentenone ring open (Terashima, 1.2.4 Scheme 6, step *vii*), however configurational or conformational assistance is evidently *not* necessary for *all* cyclization methods, as shown by the success of this Tsuji-Trost reaction.

The utility of the of the Nazarov reaction for preparation of the substituted cyclopentenone ring was again proven, however, the major drawback of this approach is that 17 individual steps are required in order to prepare the precursor for this reaction. This situation was later addressed by Song (see 1.2.16).

1.2.16 Song's Synthesis (formal total, racemic) - 2011

The synthesis published by Song's group[24] draws upon that of Frontier and is shown in Scheme 23. The pyrrole-side side chain was first installed (Scheme 23, steps *iii, iv*) by acylation in TFAA, as by Frontier, however, in this case, a terminal double bond was used as the 'handle' for later elaboration.



i) Pyrrolidine, AcOH, *i*-BuCHO, 93%; ii) TFA,DCM, 99%; iii) 6-heptenoic acid, TFAA, DCE, 99% iv) BH_3.*t*-BuNH_2, $AlCl_3$, DCM 66%; v) **189,192,** TFAA, $FeCl_3$, DCE, 75%; vi) Grubbs' catalyst, allyl acetate 79%; vii) $Pd(OAc)_2$ dppe,THF 38%

Scheme 23

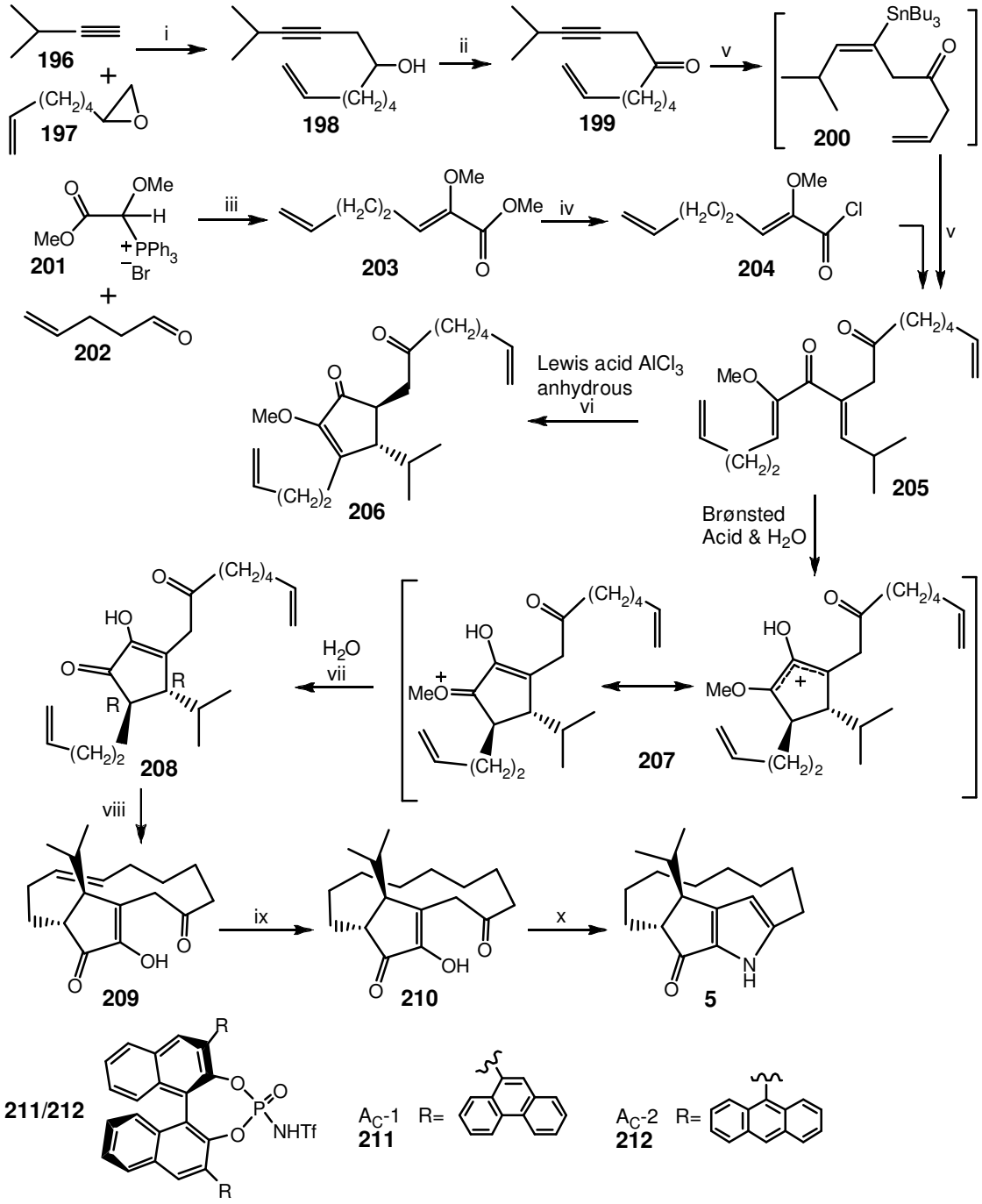
The issue of the inconvenient length of Frontier's synthesis was addressed by introducing convergency, the framework of the isopropyl-substituted side of the cyclopentenone ring being first assembled (Scheme 23, steps *i,ii*) as **189.** Coupling of **189** to the remaining α-position of the pyrrole portion of **192** proved sluggish in TFAA. Tandem acylation/Nazarov cyclization was therefore attempted, on the grounds that Lewis acids are known catalysts both for acylations and for Nazarov cyclizations. Use of Frontier's $Sc(OTf)_3$ catalyst system led to 'hydration of the double bond' (the authors do not specify which one), however TFAA and $FeCl_3$ gave a 75% yield of **194**. This

tandem acylation/cyclization procedure shortened the synthesis still further. Installation of the allylic acetoxy function required for the Tsuji-Trost cyclization was achieved by metathesis (step *vi*) with allyl acetate, after which the synthesis followed that of Frontier.

Overall, this gave a very concise synthesis, well-adapted to the preparation of analogues if desired, beginning from inexpensive starting materials. Some ‘tuning’ of conditions for the Nazarov reaction was required (as was also reported by Frontier and by Occhiato). The Nazarov cyclization (in this application at least) would appear to be rather sensitive to variations in reaction conditions.

1.2.17 Flynn's Synthesis (formal total, chiral) - 2012

Flynn and Kerr's synthesis of 2012 is the most recent,[46] and used an unusual approach to installation of chirality (Scheme 21).



i) *n*-BuLi, $BF_3.OEt_2$ 80%; ii) Dess Martin Periodinane, 80%; iii) DBU, THF, H_2O, 80%; iv) a) LiOH,THF, b) oxalyl chloride 97%; v) a) $Pd(PPh_3)_4$, $HSnBu_3$ (slow addition); b) **204** + Copper (I) thiophene-2-carboxylate, 65%; vi) $AlCl_3$ (lewis acid, anhydrous cond.) vii) A_c-2 (**212)** (chiral Brønsted acid), CCl_4, 91%, 82% *ee;* viii) Grubbs' catalyst 72%; ix) Pd/H_2 H_2 99%, 82% ee, x) NH_4OAc, $Ti(O\textit{i}\text{-}Pr)_4$, EtCOOH, 56% 95%ee.

Scheme 24

The synthesis was convergent, the preparations of **199** and **204** were unremarkable, however the one-pot coupling (previously published by Flynn)[47] was particularly unusual. Tributyltin hydride was added *syn* across the triple bond catalysed by Pd(0) to give the stannane **200.** The acid chloride **204** and copper(I)thiophene-2-carboxylate were then added, to give the Nazarov precursor **205**. Copper (I) acts as a co-catalyst for the Stille coupling, and the thiophene-2-carboxylate salt has the merit of being readily soluble in dichloromethane.

The manner of performing the Nazarov reaction was also found to be critical. Under Lewis Acid conditions ($AlCl_3$) the reaction gave the cyclopentenone **206**, the stereochemistry of which is not particularly useful. However, use of a Brønsted acid (in this case, damp methanesulfonic acid) gave **208**, due to hydrolytic trapping of the intermediate cation **207**. This resulted in the isopropyl and $(CH_2)_2CH=CH_2$ ending up in the desired *threo* configuration. The use of damp methanesulfonic acid resulted in **208** being obtained in achiral form; the reaction is diastereoselective, but not enantioselective. However, replacing methanesulphonic acid with a chiral, hindered, Brønsted acid such as A_c-1 **211** or A_c-2 **212** (5 mol % in marginally damp solvent), resulted in the chiral compound **208** being obtained in >90% yield and 82% *ee*. Macrocyclization (Scheme 23, step *viii*) was effected by Grubbs RCM, the unwanted double bond was removed (step *ix*) by hydrogenation, and the *ee* of the hydrogenated product **210** could be improved to 95% by preferential recrystallization of the racemate, prior to the final closure (step *x*) of the pyrrole ring. Overall this synthesis has the merits of being concise, convergent, and chiral.

1.2.18 Summary of Macrocyclizations

The various conditions that have been successfully employed for macrocyclization are summarized in Table 2 (below)

	Order of ring closure			Method of macro-cycle closure	Configurational or conformational assistance of macrocylization?
	Cyclo-pent-enone	Pyrrole	Macro-cycle		
Fürstner 2nd	3	2	1	RCM	None: pyrrole and cyclo-pentenone rings both still open
Boger	3	1	2	RCM	None: cyclopentenone still open
Tius 1st & 2nd	1	3	2	RCM	None: pyrrole open
Flynn	1	3	2	RCM	None: pyrrole open
Fuchs	2	1	3	RCM	Conformational: from TIPSO bicycle closed & planar
Hiemstra	2	1	3	RCM	Conformational: from SO_2Ph in side chain. Configurational: bicycle 'bent' but fully closed
Frontier	2	1	3	Tsuji-Trost	None: bicycle closed and planar
Terashima	3	1	2	Nucl carbanion	Configurational: *cis* bond in side-chain. Cyclopentenone still open
Fürstner 1st	3	2	1	Nucl carbanion	None: cyclopentenone and pyrrole rings both open
Robertson	1	3	2	Radical	Configurational: αβ-unsaturated ketone in side-chain, pyrrole ring open
Trost	2	3	1	N/A	Macrocycle by ring expansion of existing macrocycle

Note Occhiato and Song are omitted as Occhiato used Fuchs macrocyclization method and Song used Frontier's method.

Table 2

To summarize Table 2, Grubbs-type RCM has proven successful when:-

1) the cyclopentenone ring *only* is still open (Boger) and

2) the pyrrole ring *only is* still open (Tius 1st & 2nd, Flynn)

3) both of these rings are still open (Fürstner 2nd).

With the bicyclic portion closed, if RCM is to be successful, some form of steric assistance is required, either conformational (Fuchs) or configurational and conformational (Hiemstra).

Nucleophilic closure (intramolecular carbanion type) is also practical (Fürstner's 1st synthesis) with *neither* the cyclopentenone *nor* the pyrrole closed. Closure of the pyrrole introduces the requirement for configurational assistance (Terashima). Frontier stated explicitly that nucleophilic closure could *not* be made to work in a system which lacked steric assistance and had the bicyclic portion closed and planar, an unsurprising result

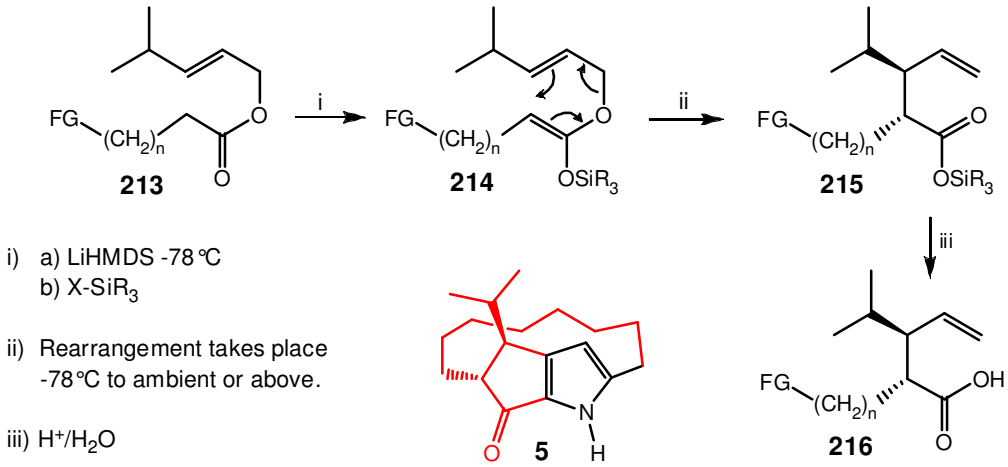
Closure by radical coupling has been proven (Robertson) to work with the pyrrole still open. The question of whether it *requires* configurational steric assistance is not really meaningful, as such assistance is intrinsic to the shape of the $\alpha\beta$-unsaturated ketone.

Closure by means of a Tsuji-Trost reaction was proven (Frontier) to be practical with the bicyclic portion closed and planar, and (remarkably) does not require steric assistance in order to work.

1.3 Previous Approaches within the Parsons Group

Much work directed towards the total synthesis of roseophilin has been done in the Parsons group over the last few years, first by Viseux[48] and later by Bouglas.[49] The overall approach is based on using the Ireland-Claisen rearrangement to install the relative stereochemistry of the *ansa*-bridge and the isopropyl group, with the intention of subsequent elaboration and cyclization

1.3.1 The Ireland-Claisen Approach



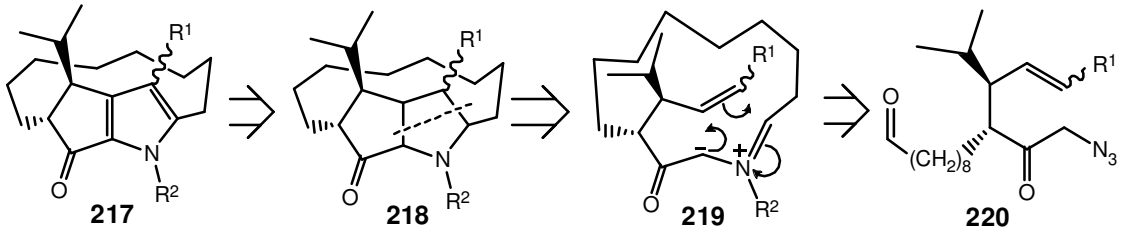
Scheme 25

The Ireland-Claisen rearrangement is shown in generic form in Scheme 25. It is one version of the general Claisen rearrangement of allyl vinyl ethers,[50] the allyl vinyl ether rearranged being the silylated enolate **214** of the ester **213**. The reaction is discussed in greater detail in 2.2.1; for present purposes the similarity between the core **5** (especially the portion of the core **5** highlighted in red in Scheme 25) and the final product **216** of the rearrangement should be noted. It will be seen that (in principle) the reaction can be used to assemble most of the cyclopentenone ring and as much of the *ansa*-bridge as desired. The starting ester **213** needs to have a functional/protecting group (FG) at the remote end as a 'handle' for further work. With this proviso, there is the option of making a 'full-length' chain (*i.e.* one long enough to form the entire *ansa*-bridge and be connected to the pyrrole ring) or a shorter chain suitable for joining (*e.g.* by metathesis) to a complementary side chain on the pyrrole side.

The synthesis of a number of long-chain fatty-acid esters and their conversion to products derived the general structure **216** by means of the Ireland-Claisen rearrangement was demonstrated by Viseux, and further investigated by Bouglas.[49]

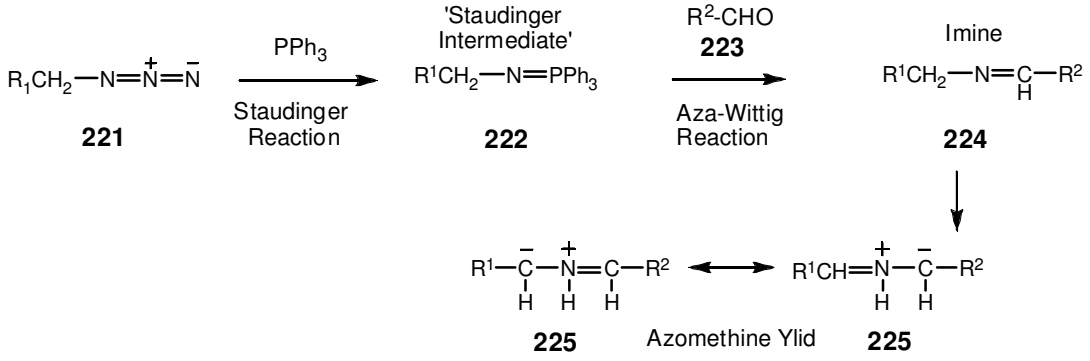
1.3.2 The Aza-Wittig and Azomethine Ylid Approach

This was the first approach to the core to be explored by Viseux. The retrosynthesis is shown in Scheme 26 below.



Scheme 26

This approach involves an intramolecular [3+2] dipolar cycloaddition using a tethered azomethine ylid **219**, derived from the azide **220** to effect closure of all three rings as a one-pot cascade reaction.

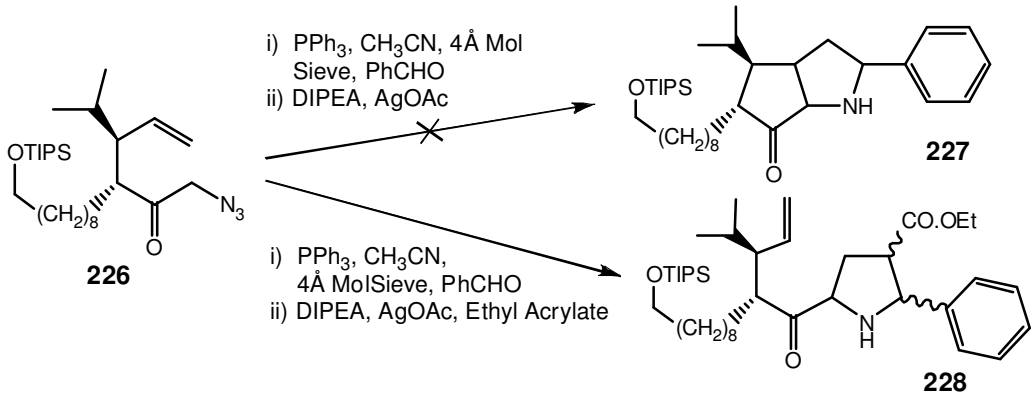


Scheme 27

Scheme 27 shows the general method for generation of an azomethine ylid in this manner. A Staudinger reaction[51] (see 2.4.3.1) is performed upon an azide **221**, to give the 'Staudinger Intermediate' **214**. This undergoes an aza-Wittig reaction[52] (see 2.4.3.2) with a suitable aldehyde **223,** to give the imine **224**, from which the azomethine

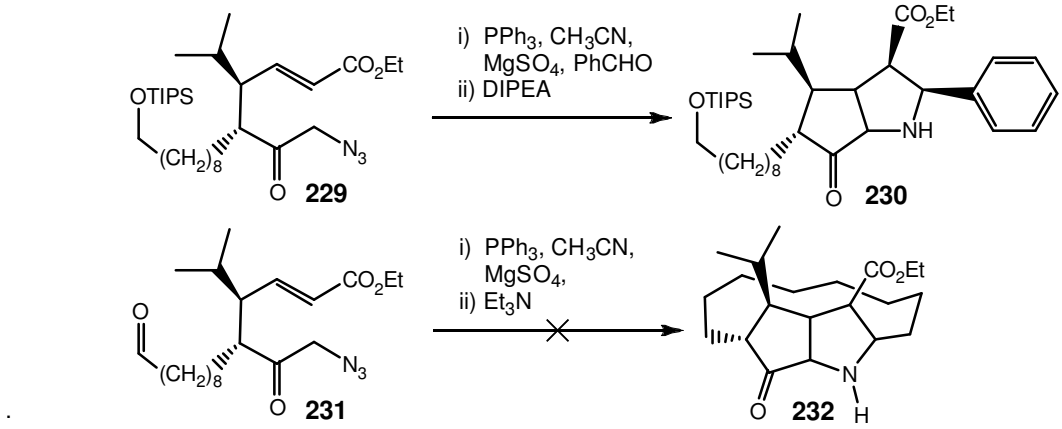
ylid **225** may be generated (see 2.4.3.2). This overall sequence was unsuccessful in effecting macrocyclization, however the results of trapping[48,53] the intermediates are highly instructive (Schemes 28 & 29).

Cyclization was attempted on **226**, in the presence of benzaldehyde as an external (*i.e.* untethered) trap for the Staudinger intermediate (Scheme 28). The benzaldehyde-based azomethine ylid failed to react with the double bond, and **227** was not obtained.



Scheme 28

However with both benzaldehyde *and* ethyl acrylate (as an external trap for the azomethine ylid) cyclization to **228** occurred. Thus the ability of the substrate to form an azomethine ylid (albeit with benzaldehyde) was proven, as was the ability of this ylid to perform a [3+2] cycloaddition on a double bond, albeit a 'best chance' double bond, both untethered and electron-deficient.



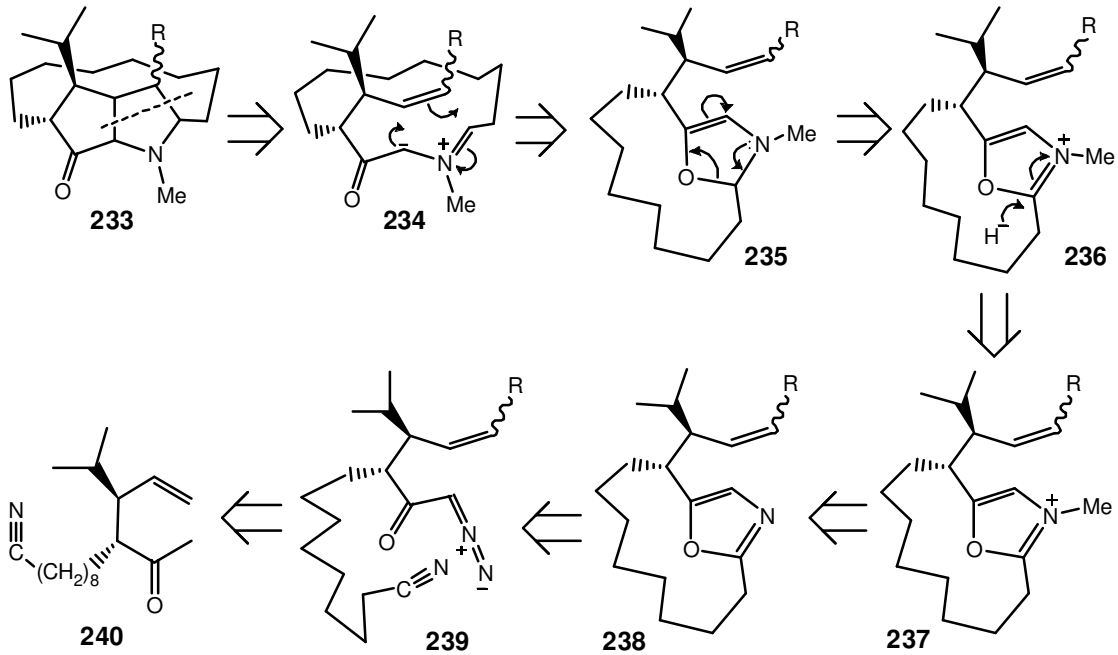
Scheme 29

The electron-rich double bond in **226** was then modified by the addition of CO_2Et to give **229** and the cyclization conditions applied (still in the presence of benzaldehyde) to give **230,** thereby confirming the viability of this approach for constructing the bicyclic moiety of the core. However, the method failed with the tethered aldehyde **231**.

The exact reasons for this are unknown. Strain and insufficient orbital overlap are possibilities, as is the ability of the imine to undergo imine/enamine tautomerism.

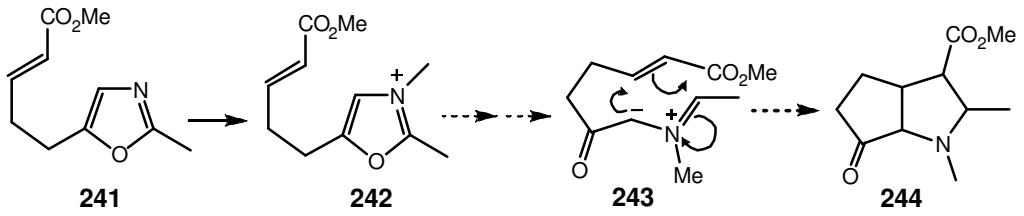
1.3.3 The Oxazole and Azomethine Ylid Approach

A second route based upon azomethine ylid cycloaddition was envisaged by Viseux, shown as retrosynthesis in Scheme 30. In this case the azomethine was to be generated from an oxazole (*via* quaternization and reduction to oxazoline, see 2.4.3.2). Oxazoles may be made from a nitrile and a diazoketone.[54] In this case, the intention was to use a tethered nitrile function, thus effecting macrocyclization *prior* to formation of the azomethine ylid. Viseux was able to prepare the cyano-ketone **240,** but was unable to obtain the diazoketone **239.**



Scheme 30

This route was revisited by Bouglas[49] as a model study (Scheme 31).



Scheme 31

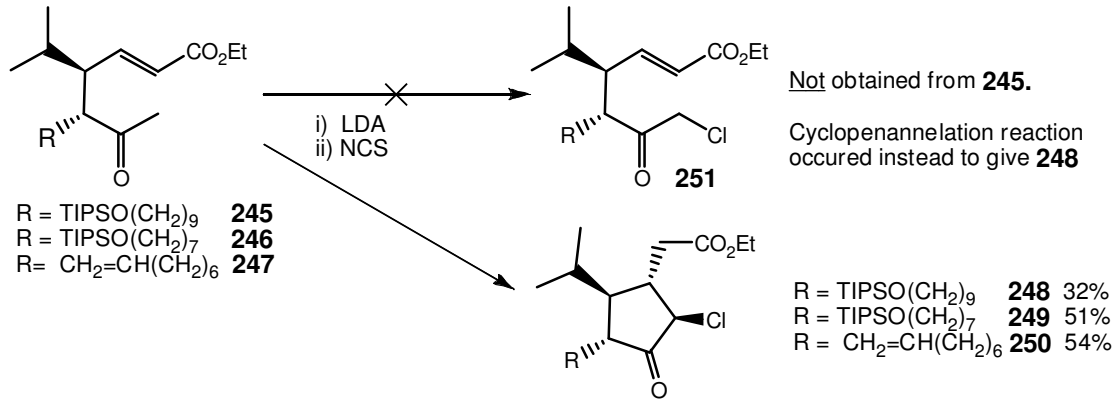
In this model system the steric constraints of the bulky isopropyl and the macrocycle are absent, and the double bond is rendered electron-deficient by the CO_2Me group, in order to give the azomethine ylid the best possible chance of effecting cyclization. The oxazole **241** was prepared, and methylated using Meerwein's salt, but all attempts at the reduction and cyclization led to decomposition. This approach was therefore discontinued.

1.3.4 The Cyclopentannelation Approach

Several approaches based upon cyclopentannelation were investigated by both Viseux and Bouglas. These may conveniently be divided into chloro-cyclopentannelation (resulting in an α-chloro cyclopentenone, with the intention of subsequently displacing the chloride with a nitrogen nucleophile) and the cyclopentannelation of substrates already containing nitrogen.

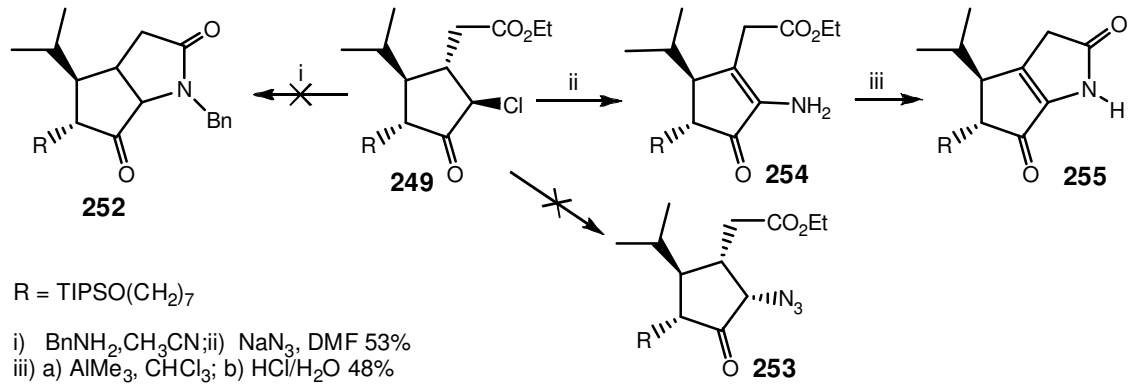
1.3.4.1 The Chloro-Cyclopentannelation Approach

Viseux's attempted α-chlorination of the ketone **245** did not give the expected product **251**, instead cyclization occurred to give α-chloro cyclopentenone **248** (Scheme 32).



Scheme 32

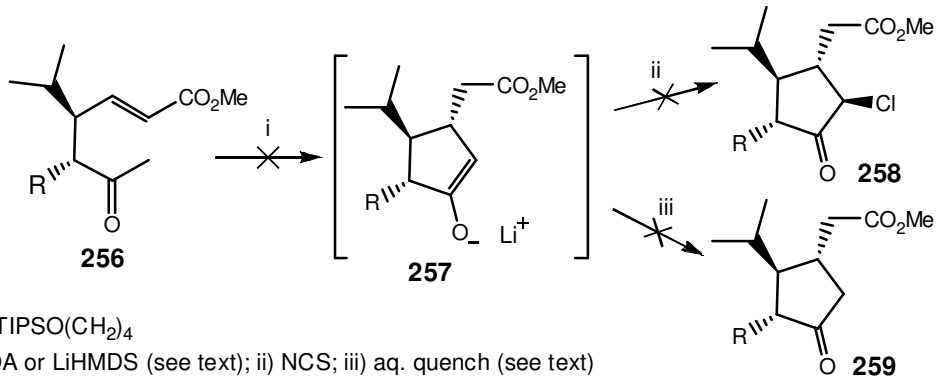
This proved repeatable on substrates **246** and **247**, giving **249** and **250** respectively, however displacement of the chlorine yielded further unexpected results (Scheme 33).



Scheme 33

Attempted cyclization of **249** (Scheme 33, step *i*) with benzylamine failed to give **252**, and attempted preparation of the azide **253** led instead to **254**. It is probable that this was due to catalysis of the decomposition of the initially-formed azide **253** by traces of dimethylamine in the DMF used as solvent. Lactamization (step *iii*) of **254** with $AlMe_3$ gave **255**. Time constraints prevented further pursuit of this approach by Viseux, in spite of its apparently great potential, and accordingly, it was further investigated by Bouglas.

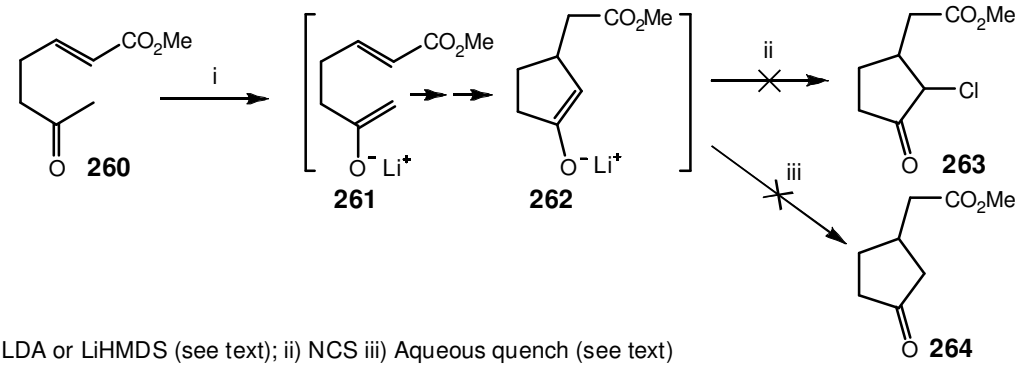
Attempted preparation, as shown in Scheme 34, of **258** from **256** (R= $TIPSO(CH_2)_4$ in this case) failed to give **258** with either LDA or LiHMDS as base. Equally surprisingly, protic quenching (as opposed to NCS) did not yield **259** as would be expected from protonation of the enolate **257**. Thus it would appear that not only the final chlorination step, but also the initial Michael addition had failed to occur.



R = $TIPSO(CH_2)_4$
i) LDA or LiHMDS (see text); ii) NCS; iii) aq. quench (see text)

Scheme 34

Bouglas therefore prepared a model system (Scheme 35).



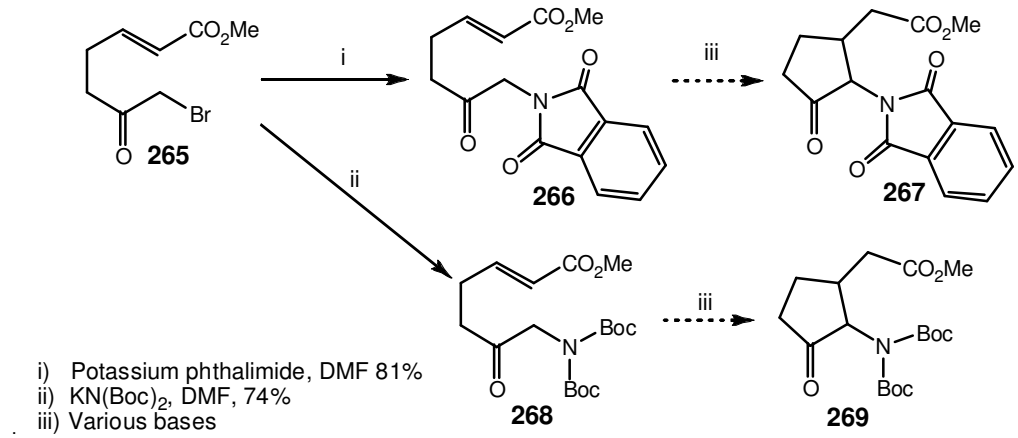
i) LDA or LiHMDS (see text); ii) NCS iii) Aqueous quench (see text)

Scheme 35

The reaction was attempted with both LiHMDS and LDA, but no chlorinated product **263** was isolated. Quenching samples with various aqueous systems (HCl, NH_4Cl, K_2CO_3) did not yield any of the unchlorinated product **264** which would have resulted from protic quenching of **262**. Only starting material and multiple minor products were obtained. It would appear from these results that successful chloro-cyclopentannelation is highly dependent on the substrate, and therefore not as generally applicable as it initially appeared. This approach was therefore abandoned.

1.3.4.2 Cyclopentannelation of Nitrogen-Containing Substrates

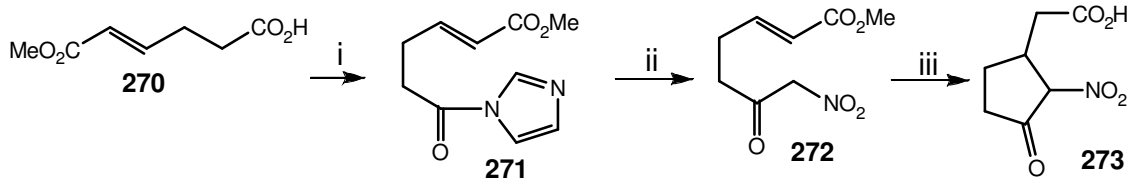
As the desirability of the chlorine in the above section was solely based upon its being replaceable by nitrogen, the possibilities of cyclization with the nitrogen already installed were investigated by Bouglas. The model system is shown in Scheme 36. The α-bromo ketone **265** was synthesised, and used to prepare the N-alkylated phthalimide **266** (the classic Gabriel synthesis)[55] and cyclization to **267** attempted with a variety of bases. None gave the desired product, and some caused decomposition.



Scheme 36

The sequence was repeated using potassium di(*tert*-butyl)imidodicarboxylate (an 'alternative Gabriel reagent', of which a number have been developed)[56] to give **268** with the intention of cyclizing this to **269**. Results with various bases were similar (no reaction or else decomposition) to those with the phthalimide based system.

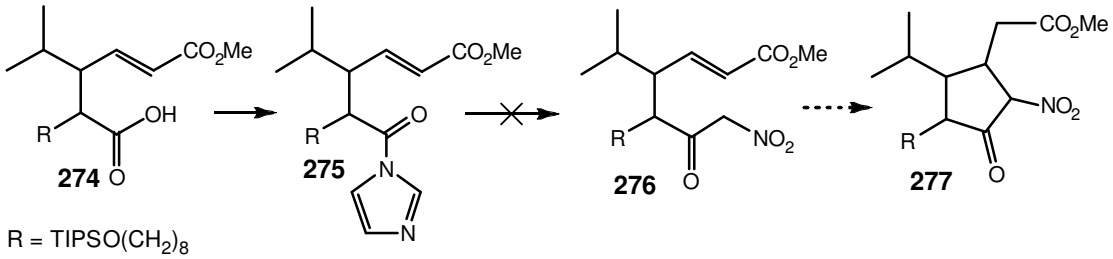
The same strategy was then applied to a model system with nitrogen installed as a nitro group (Scheme 37). Cyclization (Scheme 37, step *iii*) to **273** was successful and proceeded in high yield.



i) CDI,THF; ii) CH_3NO_2, KO^{t}Bu (79% 2 steps); iii) DBU, CH_3CN (93%)

Scheme 37

Whilst cyclization was successful in the model system, it was ineffective in the more-hindered real system (Scheme 38). Whilst the acylimidazole **275** (analogous to **271**) appeared to be formed, it would not couple with the anion of nitromethane.

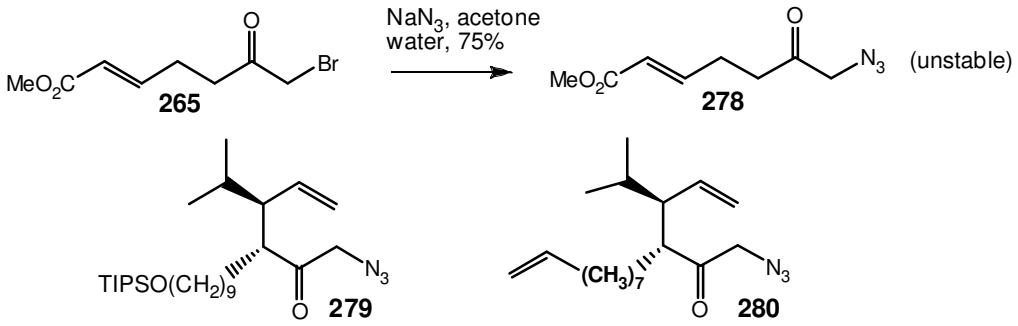


R = TIPSO$(CH_2)_8$

i) CDI,THF ii) CH_3NO_2, KO^{t}Bu

Scheme 38

Introduction of nitrogen into the model system as azide was also tried (Scheme 39).

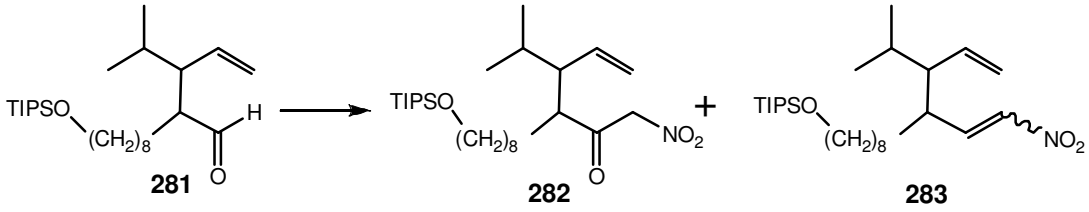


Scheme 39

Unfortunately this proved impractical as the azide **278** was too unstable to be properly characterized. The present author regards this as surprising, as analogous azides

based on the 'real' system *e.g.* **279** (made by Viseux) and **280**, (see 2.4.5) may be isolated and characterized.

Bouglas also conducted preliminary investigations (TLC-scale reactions) into introducing the nitro function by means of the Henry reaction[57] using nitromethane and various bases (Scheme 40). The nitro-compounds **282** and **283** were identified by mass spectrometry, but not fully characterized. The question of the practicality of this approach therefore remains open.

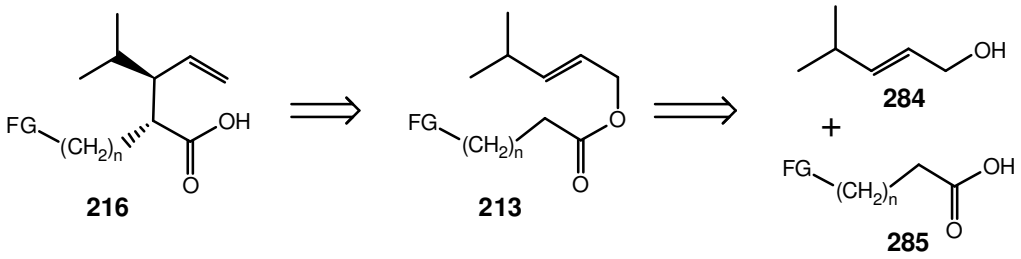


Scheme 40

Chapter 2 Results and Discussion

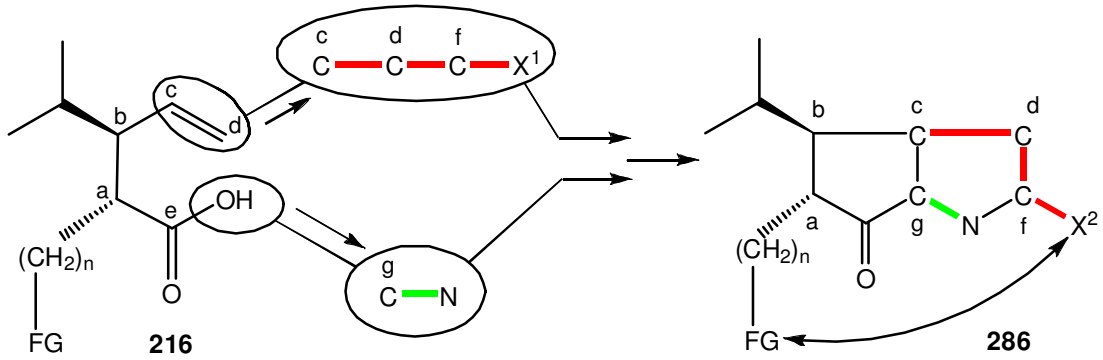
2.1 Initial General Retrosynthesis

The aim of this project was to build upon the work of already done in this group (by Parsons, Viseux and Bouglas), with the intention of developing the Ireland-Claisen rearrangement approach into a viable synthesis of roseophilin. The key step is shown in retrosynthesis form in Scheme 41.



Scheme 41

Subsequent to the rearrangement, there are many options for elaboration of the molecule to give a bicyclic system, and for effecting closure of the macrocycle by 'wrapping around' the side-chain. A number of these have already been discussed (1.3). These are summarized in 'skeleton' form in Scheme 42



Scheme 42

Referring to Scheme 42, if one considers the generic rearranged acid **216** it will be seen that the two-carbon section '*cd*' needs to be elaborated (without disturbing the stereocentre at *b*) into a three-carbon unit '*cdfX*^{1}', highlighted in red. *X*^{1} needs to be a functional group that will allow closure of the nitrogen-containing ring and still leave a useful functional group *X*^{2} at 'f' as a 'handle' for macrocyclization.

The carboxyl (carbon '*e*') requires homologation; the hydroxyl needs to be replaced (directly or otherwise) by fragment '*g*-N', highlighted in green, and this must be performed without disturbing the stereocentre at 'a'. That these fragments should be selected to facilitate both formation of the '*c-g'* bond (*i.e.* cyclopentannelation) and the closure of the pyrrole ring is self-evident.

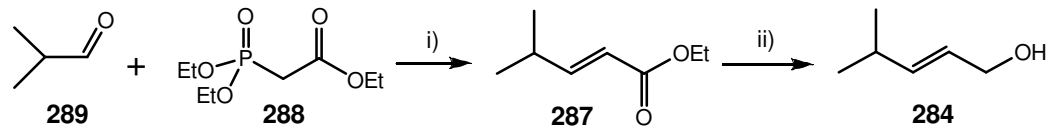
2.1.1 Synthesis of the Ireland-Claisen Precursors (General)

Referring back to Scheme 41, it will be seen that whilst the straight-chain acid **285** is shown as generic (as the length of the chain and nature of the terminal substituent FG may need to be varied), the requirement for the allylic alcohol **284**, *E*-4-methyl-pent-2,3-enol is absolute (see 2.2.1). Devising a route for bulk production of this material was therefore the author's first priority.

The next priority was to develop a bulk preparation of a suitable substituted acid **216** in quantity, to allow as wide variety of reactions as possible to be performed upon it.

It was decided from the outset to give priority to the development of efficient methodology for the bulk production of the key intermediates, *i.e.* the development of robust, scaleable reactions, with avoidance of chromatography wherever possible, the rationale being that the time spent optimizing a bulk route would subsequently pay back in scope for novel chemistry.

2.1.1.1 Synthesis of E-Ethyl-4-Methyl-pent-2-enoate **287**



289 **288** **287** **284**

i) HWE reaction, 85-94%, basic conditions. See 2.1.1.2.1
ii) DIBAL reduction, 83-91%, See 2.1.2

Scheme 43

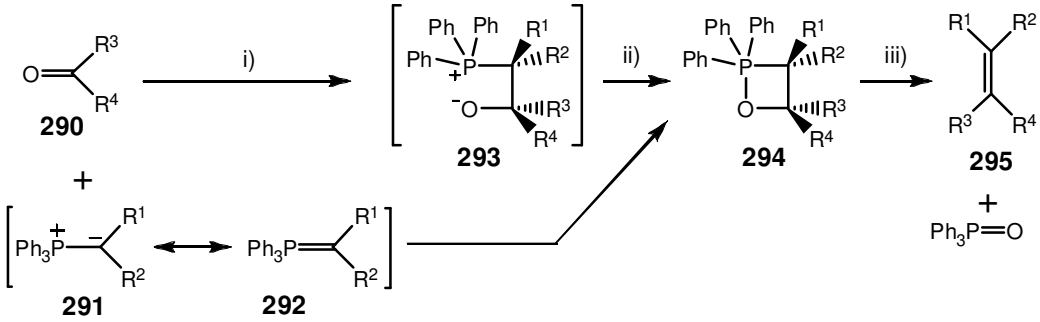
Both Viseux and Bouglas prepared **284** by the route shown in Scheme 43. Both workers used chromatography for purification at both stages. It should be stressed that the *E*-isomer of **284** is required, in a state of high diastereomeric purity (see 2.2.1).

The first step is a Horner-Wadsworth-Emmons (commonly and hereafter abbreviated to HWE) reaction, the second is a hydride reduction, which will be discussed in 2.1.2.

2.1.1.2 The Horner Wadsworth Emmons (HWE) Reaction

The HWE reaction was selected for this application on the basis of *E*-selectivity and economy. It is one of a group of closely related reactions of nucleophilic organophosphorus reagents widely used for the conversion of carbonyl groups to alkenes, which include the Wittig and Wittig-Horner (or just Horner) reaction. There is much inconsistency in the literature on nomenclature, and the above names seem to be currently the most commonly used. Essentially there are a number of 'Wittig type', or 'modified Wittig' reactions of organophosphorus compounds with a negative charge on the carbon adjacent to the phosphorus, named after their discoverers/developers, Wittig, Horner, Wadsworth and Emmons. The first two variants will only briefly be covered here.

The 'classic Wittig' reaction is shown in Scheme 44.



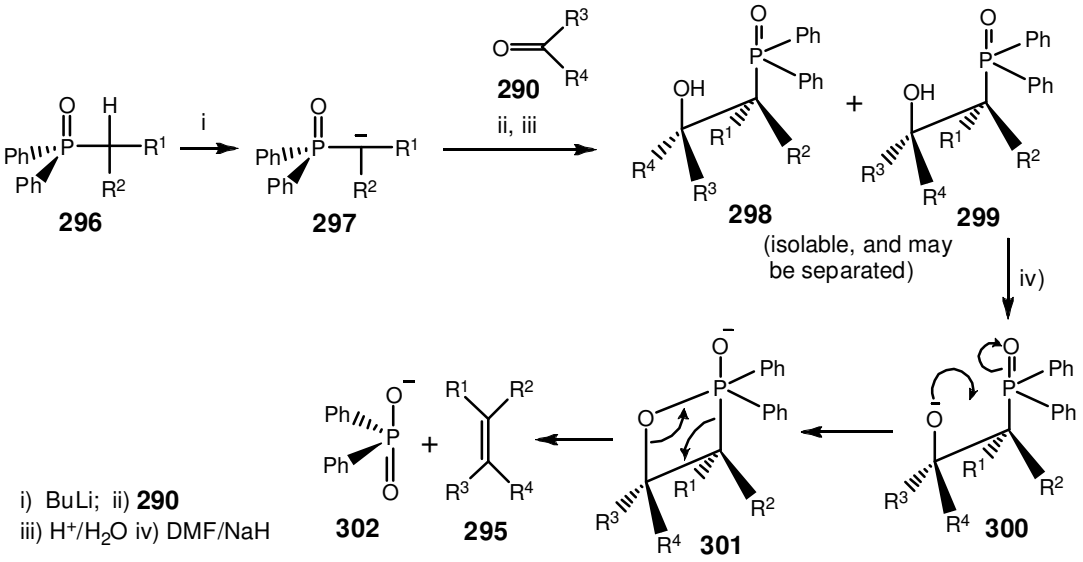
Scheme 44

There has been much investigation of the mechanism since its discovery by Wittig in 1954.[58] Deprotonation of a quaternary phosphonium salt (usually by BuLi or similar strong base) gives the Wittig reagent, which can be regarded as a hybrid of the ylid structure **291** and the phosphorane **292**. Initially, the reaction was regarded as nucleophilic attack on the carbonyl by the anionic portion of the ylid **291**, with formation of the betaine **293**, which cyclizes to the oxaphosphetane **294** with subsequent decomposes to the alkene (5). Alternatively, the reaction may be regarded as a cycloaddition by the phosphorane **292** to the carbonyl, to give the oxaphosphetane **294** directly. Whilst oxephosphetanes have been detected in Wittig reactions, and their participation appears beyond doubt, the participation of betaines is dubious. It has been shown[59] that the results of a Wittig reaction, and the behaviour of the equivalent 'genuine' betaine (generated from the corresponding β–hydroxy phosphonium salt)

differ. There is little evidence for the intermediacy of the betaine in most cases, and the cycloaddition mechanism is currently favoured. However, in 1998, Neumann and Berger[60] showed spectroscopic evidence of a betaine in a Wittig reaction. The mechanism has evidently not been 100% elucidated.

Whilst the Wittig reaction is generally *Z*-selective, the *E/Z* ratio of the products may be controlled by selection of reagents and conditions. Triphenylphosphine (or equivalent triaryl phosphine) is the unavoidable by-product, and removal is not necessarily straightforward.

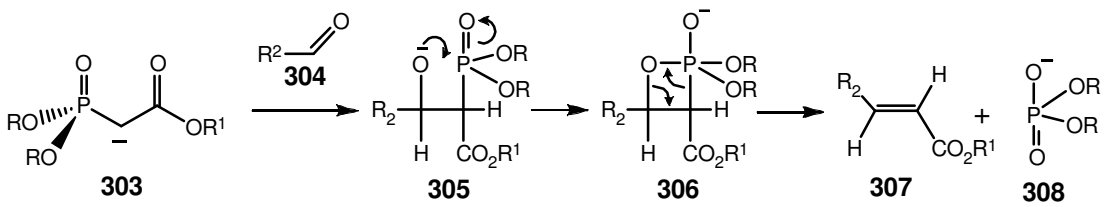
The Wittig-Horner[61] reaction is shown in Scheme 45.



Scheme 45

In this case the reagent **297** is prepared from an alkyl-diaryl phosphine oxide **296** by α-deprotonation, usually with BuLi, and the initial product is an alkoxide, analogous to the betaine **293** discussed above. Work-up at this stage gives the diastereomeric alcohols **298** and **299** derived from the *syn*-and *anti* alkoxides.[62] These are stable, and may be separated if necessary or desirable, which is an advantage of this procedure over the Wittig. Treatment of a pure diastereomer with sodium hydride in DMF gives the pure alkene **295** by elimination of the diarylphosphinate anion **302**. Elimination is *syn*, presumably *via* a four-membered oxaphosphetane species **301** as shown. The diarylphosphinates **302** are usually water soluble, a further advantage over the Wittig reaction.

The final variant to be discussed is the HWE reaction, which is shown in outline form in Scheme 46.



Scheme 46

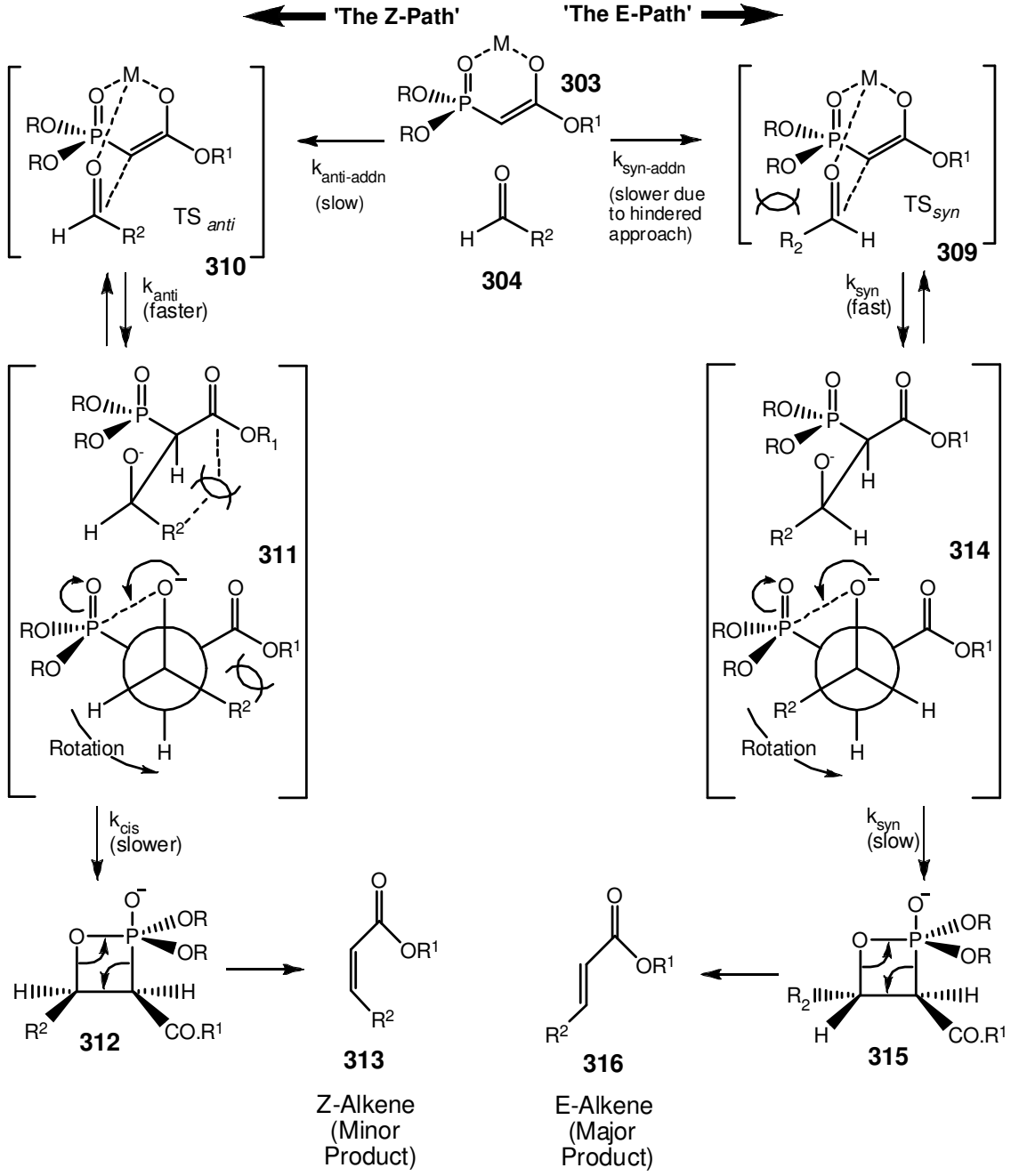
This was described by Horner and co-workers,[61] and further developed by Wadsworth and Emmons.[63] The organophosphorus component is a stabilized carbanion **303** derived from a phosphonate with an electron-withdrawing group (usually C=O or C≡N) β to the phosphorus, resulting in an 'active methylene' system. This is more acidic than the α-protons of phosphonium salts or phosphine oxides discussed above, thus milder, less basic conditions can be employed.

This is a major advantage with sensitive substrates, and the carbanions are more nucleophilic than the phosphonium ylids, hence they react readily with ketones as well as aldehydes, the ylids being rather sluggish in this respect. They do not, however, usually attack esters. The by-product is the di-alkyl phosphonate salt **308** which is usually water-soluble, and can be removed by an aqueous wash.

The mechanism has been extensively studied, and may be summarized in Scheme 47,[63,64,65] which shows the two possible pathways leading to the *E*- and *Z* isomers **316** and **313**.

The selectivity is the cumulative effect of a number of steric factors on various steps, some affecting the equilibrium position of reversible reactions, others affecting the reaction rate. The formation of either transition state (**310** or **309**) involves coordination of the oxygen of the incoming aldehyde **304** to the metal ion, controlling the orientation of the aldehyde **304** as it approaches the phosphonate anion **303.** However, the approach of the aldehyde **304** to the phosphonate anion **303** *en route* to the transition state for *syn*-addition, TS_{syn} **309** is more hindered than that leading to *anti*-addition, TS_{anti} **310** due to interference between the OR groups on the phosphonate group and R^2 on the approaching aldehyde. This route is therefore disfavoured, *syn*-addition being slower.

However once bonding has occurred, (to give the alkoxides **314** (from **309** *via syn*-addition), and **311** (from **310** *via anti*-addition), the situation with regard to proceeding further is very different. Rotation needs to occur about the bond αβ to the phosphorus (see **311** and **314** Newman projections) in order for the alkoxide oxygen and the phosphorus to become coplanar and permit formation of the oxaphosphetanes. It will be seen that there is hindrance to rotation in **311** (R^2 to $CO.OR^1$) but not in **314**.

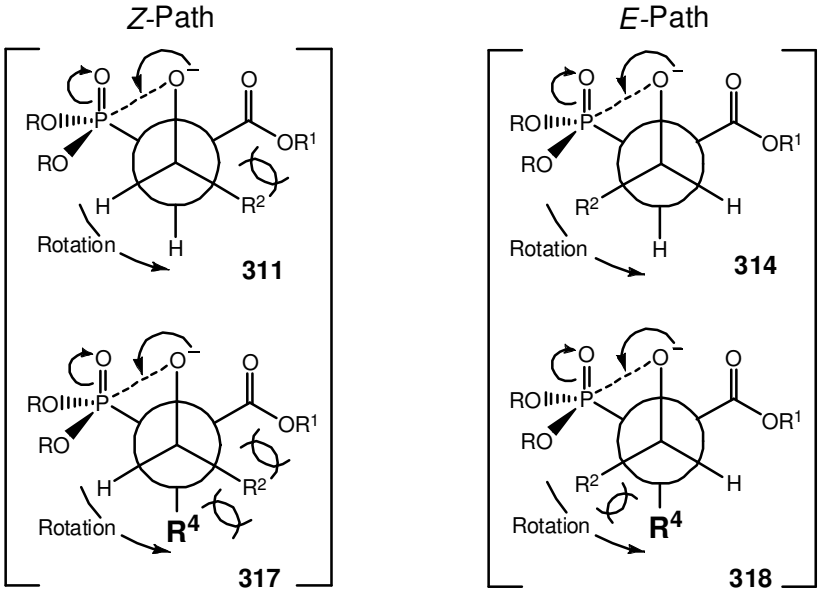


Scheme 47

Once rotation in either **311** or **314** has proceeded to the point of the phosphonate group and alkoxide-oxygen being coplanar, formation of the oxaphosphetanes **312** and **315** can occur, followed by their decomposition to the alkenes **313** and **316**.

The experimental evidence for this is extensive. The reversibility of formation of the alkoxides **311** and **314** has been proven.[66] Increasing the bulk of the aldehyde favours E-selectivity,[67] as does increasing the bulk of the alkoxy groups (OR) on the phosphonate moiety.[68]

Conversely, additional substitution at the carbonyl (the aldehyde being replaced with a series of alkyl aryl ketones),[69] increases the proportion of *Z*-products, especially with *o*-substituents on the aryl.



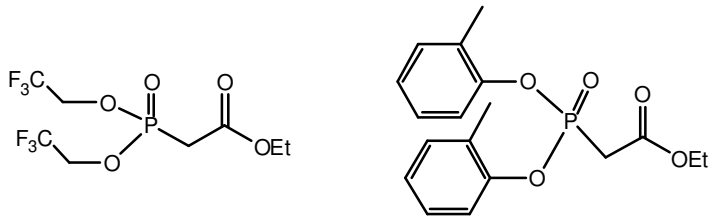
Scheme 48

Scheme 48 shows the effect of substitution (R^4) at the α-position of the phosphonate. On the *Z*-path it will be seen that **317** is little more hindered with regard to rotation than **311**; there is already a large steric interaction between R^2 and R^1, and the interaction between the hydrogen and R^4 makes little difference. However (on the *E*-path) in **305** there is a steric clash between R^2 and R^4, which is not present in **314**. The *E*-path is therefore less favourable than in **314.** These are in accordance with experimental results.[70]

With the advent of computer modelling, the various steric factors were modelled by Ando[71] in 1999, who calculated the Gibbs free energy for the various intermediates and

transition states for the reaction of the lithium anion of trimethyl phosphonoacetate with acetaldehyde, solvated with dimethyl ether. These were also in accordance with the experimental results. There were two energy maxima in each (*Z* or *E*) path. The first were at the transition states for initial addition, **310** and **311** with the *syn*-transition state **309** being of higher energy, and therefore disfavoured. The highest energy points were the transition states for formation of the oxaphosphetanes, *i.e.* overcoming the barrier to rotation of the alkoxides **311** and **314**, after which the *E*-path intermediates and transition states were all lower in energy than those of the *Z*-path, as expected.

It should also be noted that intentionally *Z*-selective versions of the HWE reaction have been developed, notably by Ando,[72] and Still and Gennari,[73] using reagents shown in Scheme 49



Still/Gennari **319** Ando **320**

Scheme 49

These are used in conjunction with highly dissociated bases ($KO^{t}Bu$ or LiHMDS) sometimes in conjunction with 18-crown-6, with the intention of reducing the coordination of the intermediates by the metal ion. In the case of **320** the bulk of the aryl groups presumably also slows the initial addition, and (more importantly) in both **319** and **320** the electron withdrawing groups accelerate the formation of the oxaphosphetanes.

Under these conditions, the initial *anti*-addition (*Z*-path to **310** is still the fastest, however once the alkoxide **311** is formed, rapid formation of the oxaphosphetane **312** and its irreversible decomposition to **313** occur. If **311** to **313** is faster than the formation of **310**, **310** will be removed as fast as it is formed, irrespective of the positions of the equilibria. Under these conditions the reaction is under the kinetic control of the initial rate of addition.

Finally, and perhaps most importantly, from a practical point of view, the economics of the HWE versus the Wittig reaction should be considered. Phosphonates are easily and inexpensively made from trialkyl phosphates *via* the Michaelis/Arbuzov reaction.[74]

Table 3 shows the price of 'CH.CO_2Et' (per mole, January 2009, Aldrich), when purchased as triethyl phosphonoacetate **288**, the pre-formed equivalent Wittig reagent **322** and the phosphonium salt **321**.

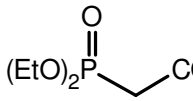
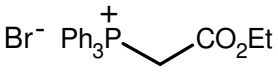
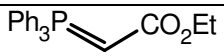
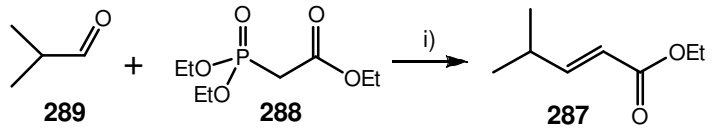
Name	Structure	N°	Payload %	Price per mole
Triethyl phosphonoacetate		**288**	38%	£66
Ethoxycarbonylmethyl triphenylphosphononium bromide		**321**	20%	£136
Carbethoxymethylene triphenylphosphorane		**322**	25%	£249

Table 3

Thus it will be seen that the HWE reaction (where applicable) is more economic than the Wittig reaction, as well as more convenient, given the water-solubility of the by-product. It is also relatively mass-efficient , 38% of **288** being 'payload'.

2.1.1.2.1 The HWE Reaction with Sodium Carbonate



i) HWE reaction, aqueous sodium carbonate

Scheme 50

Previous workers[48,49] had reported yields of 85-94% and E:Z ratios of 9:1 using aqueous saturated solution/slurry of sodium carbonate. The isomers had been separated by chromatography. These conditions were therefore tried, and the results are summarized in Table 4

Entry	Method	Scale*	Yield	Comments
1	Aqueous Sodium Carbonate	0.187 mol	44.1% (97% GC) + 6% (mixed E/Z isomers)	Aldehyde in excess (1.29 eq) Crude E/Z 8.3:1. Purification by chromatography (ether/hexane) Reaction set solid, due to crystallization of the sodium carbonate. Reaction run for 4 days
2	Aqueous Sodium Carbonate	0.187 mol	9.7% (pure by GC) + 13% (mixed E/Z isomers)	Aldehyde in slight excess (1.06eq) crude E/Z ND Purification by chromatography ether/hexane Reaction run for 5 days.
3	Aqueous Sodium Carbonate	0.455 mol	23% (pure by GC) + 34% (mixed E/Z isomers)	Slight excess phosphonate (1.08 eq). Set solid repeatedly. Reaction run for 5 days.
4	Aqueous Sodium Carbonate	0.441 mol	35% (>96% by GC) chrom+ distil	Slight excess phosphonate (1.05eq).Reaction did not set solid. Purification by combination of distillation and chromatography

* of limiting reagent

Table 4

A number of drawbacks to this reaction were immediately apparent. The yields obtained were lower than those previously reported. The most troublesome feature was that the reaction was slow, and the triphasic (organic, aqueous and solid carbonate phases) reaction medium had a tendency to crystallize and to set solid with small shifts in ambient temperature. Whilst with particularly vigorous and powerful agitation, this would have been less of a problem, the best stirrer available was of borderline efficacy, thereby rendering the reaction capricious.

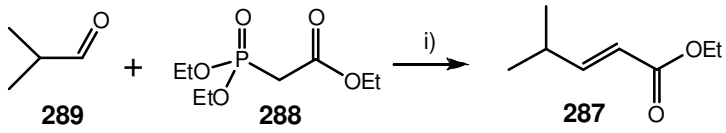
Enquiry[75] elicited that some of the original work had been performed in a reactor with an integral stirrer. Such stirrers are usually of fairly high torque and therefore reasonably constant speed, and such reactors can maintain a constant temperature. The author's experience of biphasic reactions[76] is that the rate of agitation can have a large effect on both the rate of reaction and the products obtained, and is a very difficult factor to quantify and to scale.

Chromatography was required, and separation was rather poor, necessitating large volumes of eluent. Separation of the isomers by conventional distillation (Vigreux column) proved unsatisfactory, as the boiling points of the isomers are very close. Much pot-residue was noted, even with previously chromatographed or distilled materials. This residue was not investigated, but was presumed to have resulted from polymerisation of the acrylic ester.

GC was established as being the most convenient method of analysis, given its sensitivity and suitability for measuring lower levels of impurities in comparison with NMR.

The view was taken that this method was not suitable for large scale preparation, given the poor and inconsistent yields and inefficiency of purification. A better reaction was therefore sought.

2.1.1.2.2 The HWE Reaction with Lithium *t*-Butoxide



i) HWE reaction, lithium *t*-butoxide

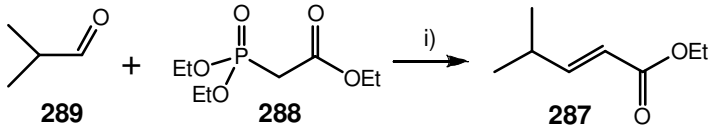
Scheme 51

A method (due to Petroski and Weisleder)[77] for a comparable HWE reaction using lithium *t*-butoxide as base was found (Scheme 51). These authors used the less-reactive triethyl-2-phosphono*propionate,* rather than the triethyl phosphono*acetate* being used in the present case. The method was applied to the present system, with minor modifications, *i.e.* lower temperature (-20°C rather than ambient temperature) and the lithium *t*-butoxide being prepared *in situ* as a 1-pot procedure using *n*-BuLi and *t*-butanol, rather than being purchased as lithium *t*-butoxide solution. A slightly milder work-up procedure (sodium bicarbonate solution, rather than plain water) was adopted, in order to buffer the excess of LiOH that would otherwise form.

The *E/Z* selectivity was much better than in the sodium carbonate version (the reaction being 95-98% *E*-selective), yields of 50-70% were obtained, the actual reaction takes about 2 hrs, rather than several days, and 14-15 g batches could readily be processed.

The issue of purification was addressed by kugelrohr distillation. The advantage of this apparatus over conventional patterns of still is that the distillation path is short, and the temperature difference between the 'pot' and the condenser is small, therefore the 'pot' temperature needed for distillation of a given material is lower than in a conventional still. This reduces losses due to polymerisation/decomposition during dwell-time at elevated temperature in the 'pot'. However, the ability to effect more than minimal fractionation is severely curtailed. With an acceptable *E/Z* ratio of product isomers, separation of the isomers of the product was no longer an issue. The distillation served to separate **287** from the excess triethyl phosphonoacetate (plus any other high boiling material), whilst losing as little as possible to polymerisation or decomposition in the process.

2.1.1.2.3 The HWE Reaction with Methyl Magnesium Bromide



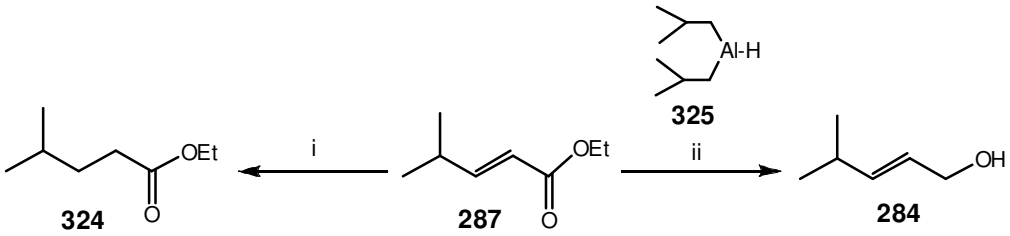
i) HWE reaction, methyl magnesium bromide

Scheme 52

After the HWE studies were started, a method using methyl magnesium bromide as base was published by Davies and co-workers,[78] the authors claiming *E:Z* ratios of 180:1 (Scheme 52). This method was tried when resynthesis of **287** was required. Yields of 84-93%, were obtained on up to 80 g scale. No traces of the *Z*-isomer **323** could be detected by GC. Final purification was effected by distillation (using a *vacuum jacketed* Vigreux column in order to keep the required pot temperature as low as practical) at 15mm.

2.1.2 Hydride Reduction of Ester **287** to 4-Methyl-Pent-2-enol **284**

Previous workers[48,49] had used DIBAL **325** in diethyl ether for this reduction, obtaining *ca* 83-91% yields, after chromatography.



i) $NaBH_4$/MeOH/THF ii) DIBAL 83-91%

Scheme 53

Sodium borohydride in methanol was tried, as a cheaper alternative to DIBAL, due to other members of the group having had previous success with similar reductions[79] (Scheme 53, step *i*). In this case, however, the product (identified by GC/MS) was the saturated ester **324**. It was therefore decided to stay with DIBAL. A stock 1M solution of DIBAL in diethyl ether was prepared from neat DIBAL, as purchased DIBAL solution has a reputation for variable quality.[79]

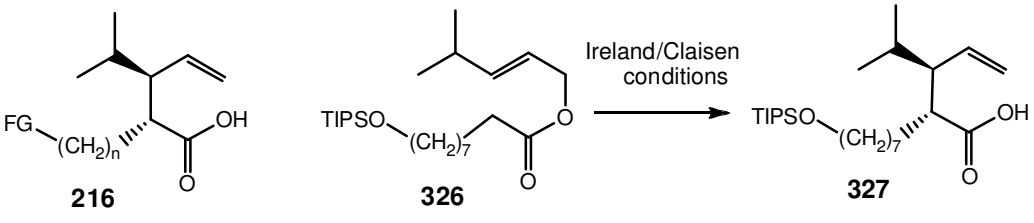
A further complication was introduced when a shortage of diethyl ether was followed by an approximately tenfold increase in its price. It was found that the diethyl ether could partially be replaced with dichloromethane to the extent of using 3:1 dichloromethane:diethyl ether as the bulk reaction solvent. The ester **287** is freely soluble in dichloromethane at room temperature, but precipitates at –70°C unless diethyl ether is used as a co-solvent.

There are various work-up procedures for use with DIBAL. An alkaline work-up aimed at producing a dry, granular, filterable precipitate was found on the Frontier group website.[80] This method is analogous to the widely-used Steinhardt work-up for $LiAlH_4$ reductions.[81] The method was tried, but gave a disappointing yield of 35%. The established[48,49] 15% aqueous sulfuric acid proved to be the best, however an hour's stirring at 20°C was required in order to give a clear biphasic system and to completely dissolve the aluminium salts and complexes.

Eventually it was determined that adding the DIBAL over 90 minutes, keeping the internal temperature below -70°C, allowing the reaction to proceed for 2-3 hrs at -78°C, then an acid work-up gave a near-quantitative yield of crude product. Chromatography being considered undesirable (due to economics and volatility of the product), batches of crude product were combined and purified by distillation, giving purified yields of >80%. Given that **284** is not an acrylic system, polymerisation should not have been a problem; there was, however, some pot-residue, which appeared (by GC) to be a complex mixture and was not further investigated.

2.1.3 Preparation of the Ireland-Claisen Precursor (*E*)-4-methylpent-2-enyl 9-(triisopropylsilyloxy)nonanoate **326**

With the availability of the allylic alcohol **284**, it was necessary to select the side-chain for the rearranged acid **327** to be used for future work, and to synthesize the appropriate long-chain acid.

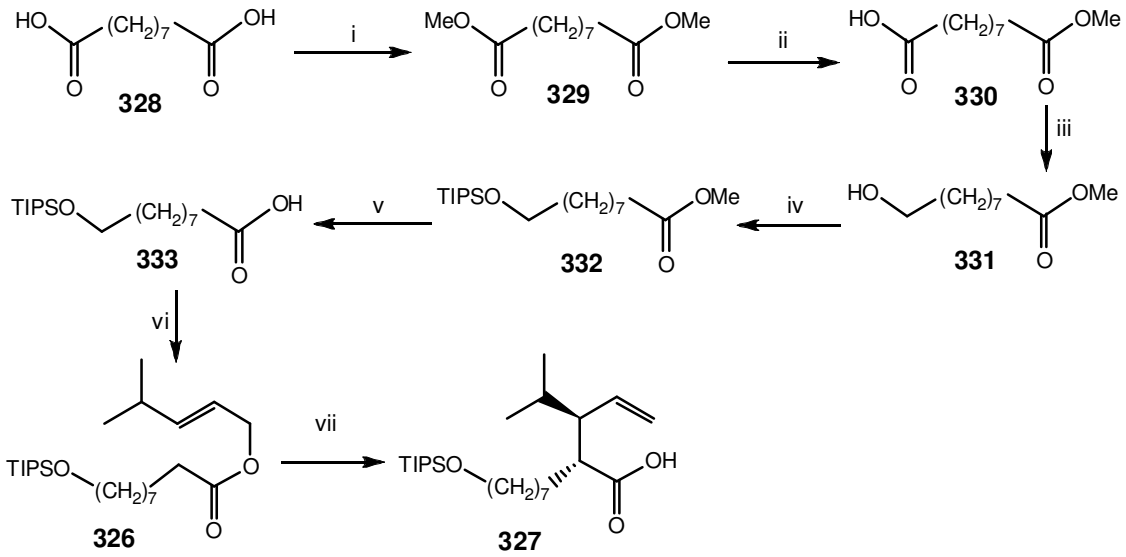


Scheme 54

Referring to Scheme 54, the side-chain TIPSO-$(CH_2)_7$ (*i.e.* the acid **327**) was selected, necessitating the preparation of the azelate-derived open-chain ester **326**.

2.1.3.1 The Azelate Route

The synthesis of the ester **326** is shown in Scheme 55.



i) H_2SO_4/MeOH, 84%; ii) a) $Ba(OH)_2$/MeOH b) H^+/H_2O (50-70%); iii) BH_3/THF 90% iv) TIPSTf v) KOH (40% 2 steps) vi) **284**, EDCI 37-55%; vii) Ireland/Claisen conditions

Scheme 55

This had been prepared by Viseux, starting from methyl hydrogen azelate **316**, (hence Scheme 55, steps *iii* to *vii* were already proven) however, as **330** was considerably more expensive than azelaic acid **328**, and bulk quantities were desired, it was decided to start from azelaic acid. The method of Rao and co-workers[82] was used for esterification (step *i*) to **329,** and was straightforward, however the selective hydrolysis[82] to give **330** merits discussion. Addition of methanolic barium hydroxide solution to a solution of **329** in methanol precipitated the barium salt of **330**, from which **330** was recovered by acidification and extraction. Whilst the yield (50-70%) was modest, acidification and extraction of the various liquors allowed azelaic acid **328** to be recovered (as a mixture free acid, mono- and di-esters) and subsequently reclaimed as dimethyl azelate. Preparation of **330** from the diacid **328** could therefore be made practically quantitative. Reduction of **330** to **331** (step iv) with BH_3 in THF proceeded cleanly in 90% yield, although traces (<2%) of nonane-1,9-diol, due to over-reduction, could be detected by GC.

TIPS protection (step *iv*) and hydrolysis of the methyl ester (step *v*) proved troublesome and time consuming. The general method of Viseux (TIPSOTf/2,6-lutidine to protect, followed by KOH/MeOH to hydrolyse the methyl ester) was followed.

It was considered that it would be more efficient to subject the mixed products of the TIPS protection (**332** plus TIPS-OH) to hydrolysis with KOH/methanol without separation of **332,** given that this would avoid one column, and that an acid should be easier to separate than a neutral compound from unwanted neutral impurities (TIPS-OH, plus probably some $TIPSO(CH_2)_9OTIPS$). The (apparently obvious) method of extracting the acid into aqueous base and attempting to wash out neutral impurities proved impractical. The sodium salt of **333** is an excellent emulsifier, which is unsurprising in view of its structural similarity to a typical soap.

TLC analysis was not particularly satisfactory, as the compounds do not contain a significant UV chromophore, and stain poorly with iodine, although PMA dip (as long as it was fresh) allowed them to be visualized reasonably well. GC was more effective for monitoring the reaction's progress.

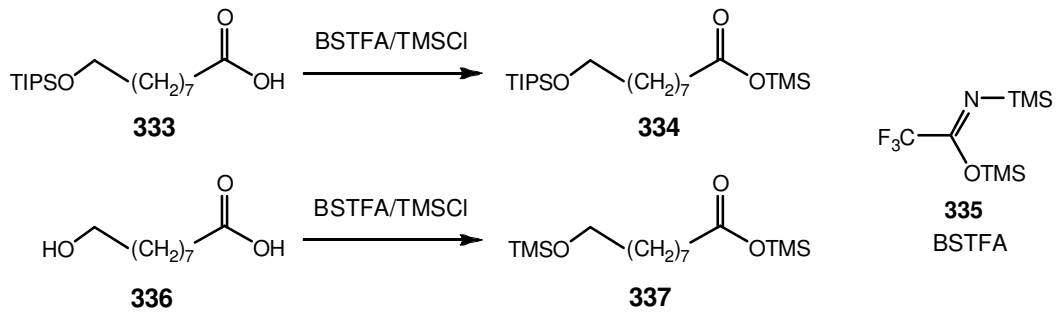
The first small 'sighting' reaction confirmed that the product was amenable to GC, hence both the formation of product and the disappearance of starting material could be observed. Each GC sample was given a 'mini-work-up', a few drops being taken,

diluted with diethyl ether, washed successively with dilute HCl, saturated sodium bicarbonate, brine, then dried by filtration (pipette filter) through anhydrous sodium sulfate. The reaction appeared fairly clean at this point.

However, after working up the whole reaction (using the published work-up, quenching with ice/2N HCl, washing successively with sodium bicarbonate solution, brine, and drying over anhydrous sodium sulfate), approx 2% of starting material had reappeared. It would appear that the TIPS protecting group is only marginally stable to 2N HCl, *i.e.* it will tolerate a brief 'mini work-up' (where it is exposed to 2N HCl for approx 30 seconds), but not for longer. Working up with citric acid, adjusting the pH to 1-2 with a few drops of HCl was found to be more satisfactory. The hydrolysis (step v) of the methyl ester was worked up in the same way.

Small-scale attempts to purify the acid on an anion exchange resin, Amberlyst A26-OH,[83] a technique which the author had previously used on highly lipophilic acids[76] were unsatisfactory, as was an attempt to purify it *via* the barium salt (compare **330**), hence the bulk of this acid was isolated by chromatography, in 47% yield over 2 steps.

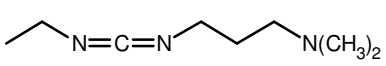
Given the similarity (and consequent of overlap of signals) of the NMR spectra of the silylated materials **332**, **333**, and **320**, NMR analysis proved rather unsatisfactory for determining impurity levels, especially given the ease of removal of TIPS. Given the success of the GC method in monitoring silylation, a GC method was therefore developed. This also raised the possibility of monitoring the Ireland-Claisen reaction by this method, given that the immediate product of the rearrangement **215** (Scheme 25) is a silyl ester of a carboxylic acid. Whilst carboxylic acids themselves are rarely (unless of low molecular weight) sufficiently volatile to be amenable to GC, their silylated (especially TMS) esters are classic derivatives for GC analysis.[84,85]



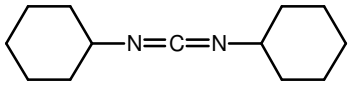
Scheme 56

Accordingly trace-scale samples of **334** and **337** were prepared by treating the respective acids **333** and **336** with a commercial derivatizing solution of BSTFA **335** c/w 1% TMSCl (Scheme 56).[86] This provided a means of checking the purified ester **320** (by quenching a sample in BSTFA/TMSCl and subjecting it to GC) for the presence of unreacted acid **333** or de-silylated acid **336**.

Coupling of **333** with **284** was effected with **338** EDCI (see Scheme 55, step *vi*), a carbodiimide coupling agent with the advantage over the more commonly-used DCC **339** that the urea by-product is rendered more water- and acid- soluble by the dimethylamino group, thereby facilitating work-up.



338 EDCI



339 DCC

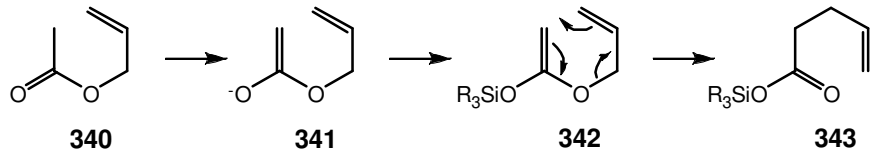
Scheme 57

Yields were unsatisfactory (55-37%), despite the fact that previous this reaction had previously[48] given a 94% yield. See also 2.2.3 and the preparation of **360**.

2.2 The Ireland-Claisen Rearrangement

2.2.1 Background and Mechanism

The Ireland-Claisen rearrangement is a [3,3] sigmatropic rearrangement of allyl esters via their silylated enolates (ketene acetals), first reported by Ireland in 1972,[87] and widely applied and studied since.[50] Unusually for a Claisen rearrangement, it is performed under basic conditions, and actual rearrangement usually takes place well below 100°C, often at ambient temperature or below. In its simplest form it may be represented as in Scheme 58.

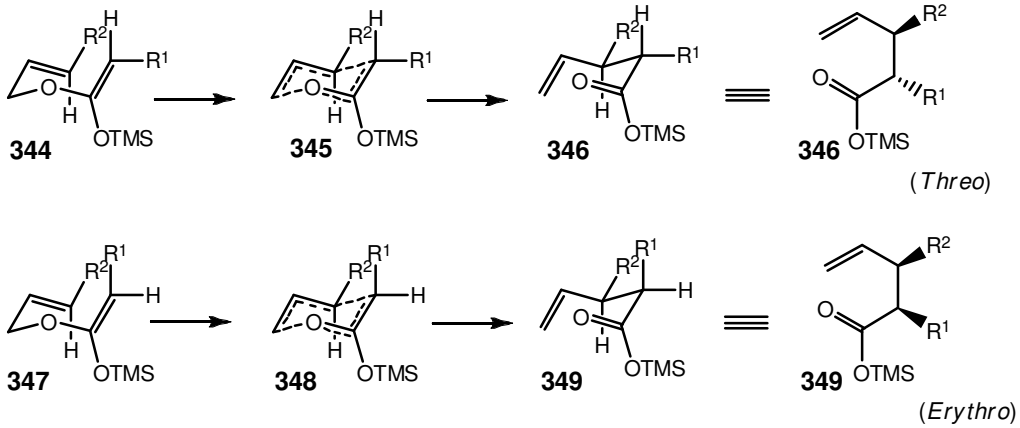


340 **341** **342** **343**

Scheme 58

The ester **340** is converted to its enolate **341** by a suitable base (usually a bulky lithium base *e.g.* LDA or LiHMDS), then the enolate is silylated (TMSCl, TBDMSCl etc) to form the silyl ketene acetal **342**. The silyl ketene acetal, being an allyl vinyl ether, undergoes the Claisen rearrangement to give the silyl ester **343** of a 4,5 unsaturated acid. The silyl ester is usually hydrolysed by an aqueous work-up.

With the ester **340** being an acetate, and the allylic moiety being unsubstituted, there are no stereochemical complications. The situation changes with the introduction of a substituent (R^1) adjacent to the carbonyl, or (R^2) upon the allylic portion (Scheme 59).

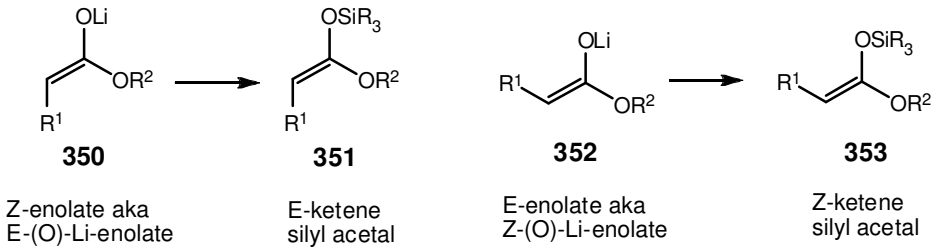


Scheme 59

The stereochemistry of the product is controlled by both the configuration of the allylic moiety and that of the ketene acetal, and by whether the reaction proceeds by a chair transition state (as shown), or *via* a boat configuration. It is important to note that the geometry of the allylic portion is pre-set by use of the appropriate allyl alcohol when preparing the starting ester **340**, hence the effort put into obtaining the allylic alcohol **284** isomerically pure. In acyclic systems, the results are consistent with the chair transition state, whilst in constrained (*i.e.* cyclic, or sterically-crowded) systems, a boat configuration may be preferred. The energy difference between the two has been calculated for allyl vinyl ether (the unhindered, unconstrained prototype system) as 9.6kJ/mol.[50]

The geometry of the ketene acetal is set by the enolization conditions, **344** and **347** being derived from the two possible enols of the *same* ester. Thus (by selecting conditions to give the *Z*- or *E*-enolate and trapping this as the silyl ketene acetal) the same product can be made from an ester of either the *cis*- or the *trans*-allylic alcohol. Equally, both the *threo* **346** and *erythro* **349** isomers can be made from the same starting material. The potential to form *E* and *Z* isomers in this manner, and the resultant versatility is the probably greatest advantage of the Ireland Claisen rearrangement from a synthetic point of view.

The conventional *E/Z* nomenclature can be unhelpful and confusing when discussing these reactions, as the substituent priorities of Li, Si, and carbon differ. The practice of referring the geometry of the enolates to the enolate oxygen (described in Reference 50 p128), whilst somewhat cumbersome, is at least unambiguous, and helpful in that *E* and *Z* do not transpose upon silylation (Scheme 60).



350 Z-enolate aka E-(O)-Li-enolate

351 E-ketene silyl acetal

352 E-enolate aka Z-(O)-Li-enolate

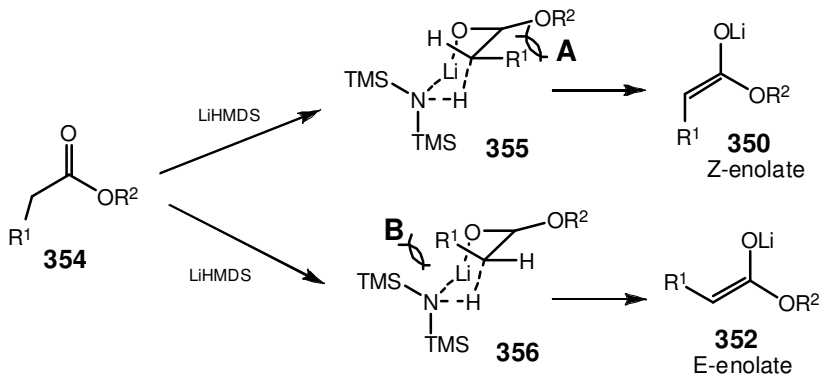
353 Z-ketene silyl acetal

Scheme 60

Using conventional nomenclature, silylation of **352**, an *E*-enolate (or *Z*-(O)-Li-enolate as preferred) gives **352** a *Z*-ketene silyl acetal.

It has been established that in neat THF with lithium amide bases, there is preferential formation of **350**, the *Z*-enolate, precursor to *E*-silyl ketene acetal **351**. Conversely, in the presence of HMPA or DMPU (which strongly solvate the lithium cation) preferential formation of **352** the *E*-enolate (precursor to the *Z*-ketene silyl acetal **353**) occurs.

To what extent the formation is under thermodynamic or kinetic control has been the subject of much investigation and debate between Corey,[88] Heathcock[89] and Ireland.[90] Referring to Scheme 61, the currently favoured explanation (primarily due to Ireland) is that, with lithium ion freely available, the transition state **355** for the formation of the *Z*-enolate **350** is favoured, as there is only a little torsional strain (at A) between R^1 and O-R^2. Conversely, in the transition state **356** for formation of the *E*-enolate, R^1 strongly interacts (at B) with the substituent (here a bulky TMS) on the nitrogen base, and this transition state is therefore disfavoured.



Scheme 61

This assumes a tight transition state (as shown), and the tighter and more highly-ordered the transition state becomes, the more significant this strain will be.

If lithium ion is not available for participation in the transition states (which is the situation where Li^+ is 'tied up' by solvation *e.g.* by DMPU or HMPA) the transition states will be looser.

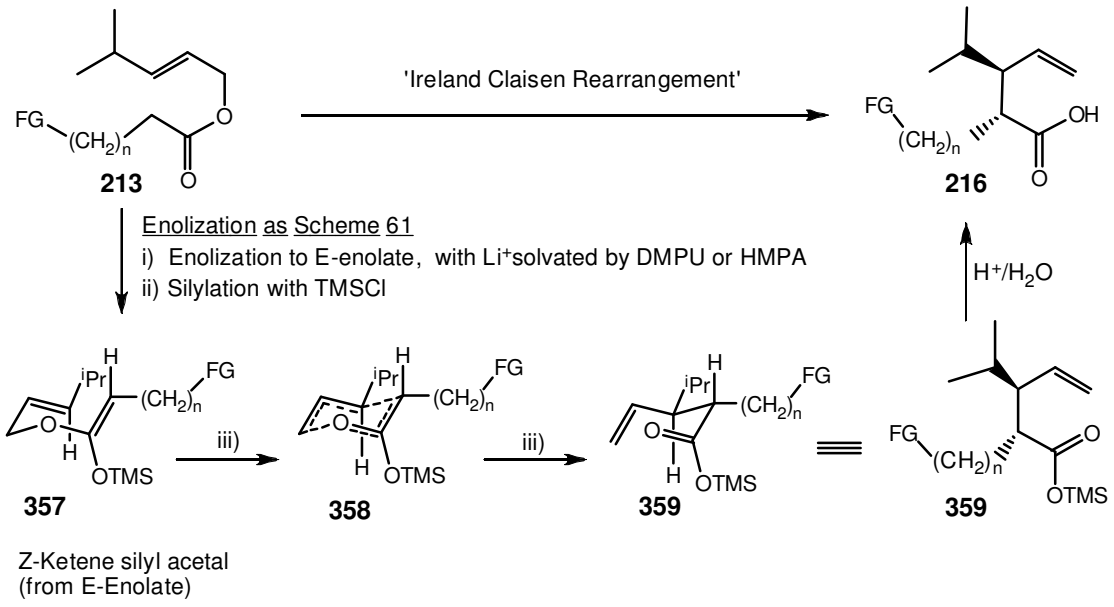
Under these circumstances the significance of interaction B between the base and the ester (which is intermolecular until formation of the TS, and becomes progressively stronger as the transition state tightens) will be greatly diminished, whilst the torsional strain A, which is largely unaffected by the formation or otherwise of the transition state

remains effectively constant. The factors favouring the formation of transition state **355** are removed, as are the factors previously disfavouring the transition state **356,** and the route leading to the *E*-enolate **352** is preferred.

Once the enol has been formed, the silylating agent (TMSCl etc) is added in order to trap the enol as the silyl ketene acetal. Whilst the enolization stage is reversible, allowing interconversion of the *E* and *Z* isomers, silylation is irreversible. Silylation should preferably be as rapid as possible, in order to 'freeze' the reaction at the equilibrium, and to preserve the carefully-established enolate geometry in the ketene silyl acetal. Thus it will be seen that by *suitable* choice of solvent system the direction of the enol formation (*E* or *Z*), thereby the configuration of the silyl ketene acetal, can be controlled at will.

Whilst this is one of the greatest advantages of the Ireland-Claisen rearrangement, it is also its greatest drawback. An *unsuitable* choice of enolization conditions leads to mixtures of diastereomers. Expressed differently, from a purely practical point of view, the reaction is extremely dependent upon substrate, solvent, and reaction conditions to the extent it may be regarded as capricious and unreliable. It is certainly not what may be termed a 'robust' reaction.

Returning to the present situation, Scheme 62 shows the desired 'real system' in generic form.



Scheme 62

The step marked 'Ireland-Claisen Rearrangement' therefore actually encompasses three steps:

i) Controlled enolization to give the desired configuration of enol.

ii) Trapping of the enol without altering its configuration

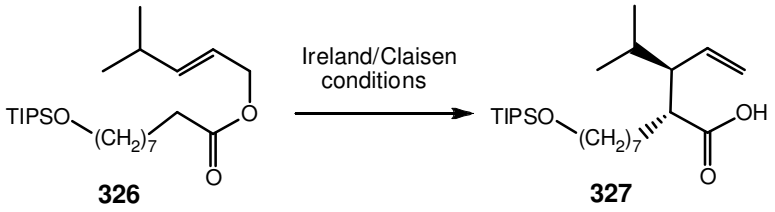
iii) Claisen rearrangement of the ketene silyl acetal

There are two constraints to be taken into consideration. The first is that in order to obtain **216**, the side-chain and the isopropyl group must end up *threo* to each other following the rearrangement. The second constraint is the geometry of the allylic portion of the starting material **213**. This geometry is fixed as it is derived from **284**.

With these constraints, it will be seen that it is necessary to prepare the *E*-enolate of the ester **213**, then trap this to give **357**, the *Z*-ketene silyl acetal. The silyl ketene acetal **357** is then required to undergo the actual Claisen rearrangement to give the silyl ester **359** which is hydrolysed upon work-up to give **216**.

With regard to the practicalities of the reaction, previous workers[91] stressed the importance of freshly distilled TMSCl, with no free hydrogen chloride (*i.e.* distilled immediately before use, from calcium hydride) in addition to the usual requirement of organolithium reactions for all solvents to be rigorously anhydrous. Et_3N or TMSTf can also be used to enhance reactivity of the TMSCl. When Et_3N (premixed with TMSCl) is used it is apparently important that any precipitated solid be removed. Temperature should be kept below –60°C during enolization and silylation otherwise the 'ordinary' Claisen condensation would become a competing reaction (see Scheme 66). DMPU needs to be scrupulously dry. The DMPU used by the author for all Ireland-Claisen condensations was purchased anhydrous (over 4Å sieve), was redistilled from calcium hydride, then stored in the dark over freshly activated 4Å molecular sieve, under nitrogen.

2.2.2 Ireland-Claisen Rearrangement of Ester **326** to (*R**)-2-((*S**)-4-methyl pent-1-en-3-yl)-9-(triisopropylsilyloxy) nonanoic acid **327**



Scheme 63

The Ireland-Claisen Rearrangement was attempted twice on this substrate. The first reaction showed no trace of a rearranged silyl ester by GC, however, as the amenability of the specific ester in question to GC is unknown, its apparent absence proves nothing. Analysis of the worked up mixture (preparative TLC and NMR) showed only starting material, and other products which were not positively identified.

The reaction was repeated with the addition of 1,2-epoxybutane as a neutral 'acid trap' *i.e.* to absorb any HCl from the excess of TMSCl used. A trace of the desired product **327** (a minor product) was detectable by NMR after preparative TLC.

Entry	Eq Li HMDS	DMPU %*	ET (minutes)	ST (minutes)	RT (hours)**	SC	Yield %	Comments
1	2	55	60	10	40	TMSTf	0	
2	2	55	60	10	24	TMSTf	Trace	Epoxybutane added as acid trap.

ET = Enolization Time ST = Silylation Time RT = Rearrangement Time

SC = Silylation Catalyst

* Approximate percentage by volume as solvent *i.e.* 100 x Vol DMPU/ (Vol DMPU + Vol THF)

** At ambient temperature in both cases

Table 5

The sample was highly impure, and the quantity only sufficient for MS, and a poor proton NMR. The latter was identified by 'fingerprinting' against a simulated authentic spectrum constructed from Viseux's data.[48]

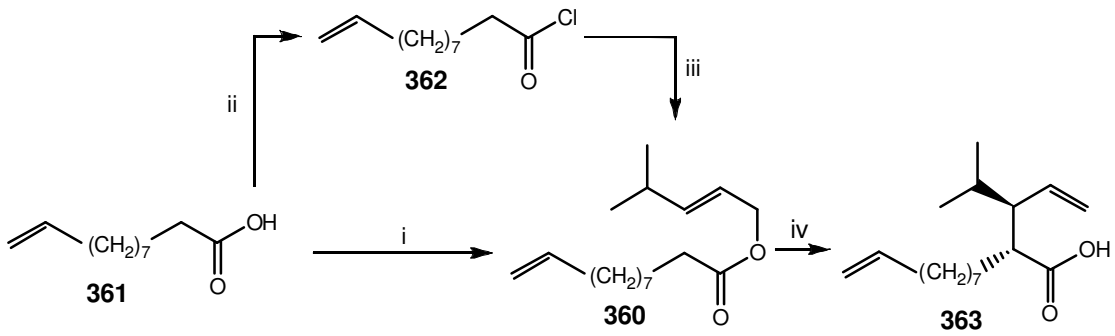
At this point is was decided to investigate the conditions required more closely by use of a model compound, in order to conserve advanced starting material.

2.2.3 Preparation of Ireland-Claisen Precursor **360**

(*E*)-4-methylpent-2-enyl undec-10-enoate

10-Undecenoic acid **361** is prepared on an industrial scale by cracking castor oil at 400°C. The acid and its salts (especially the zinc salt) are widely used as topical antifungals[92] and for treatment of psoriasis.[93] Consequently it is commercially available in large quantities and is inexpensive.

Given the above, the ester **360** was selected as a substrate for development of the Ireland-Claisen rearrangement. The terminal double bond is capable of modification, but is not as fragile as O-TIPS. The ester **360**, therefore was considered suitable as an accessible and robust model, and because the product **363** would be an acceptable (if not ideal) intermediate for further work.

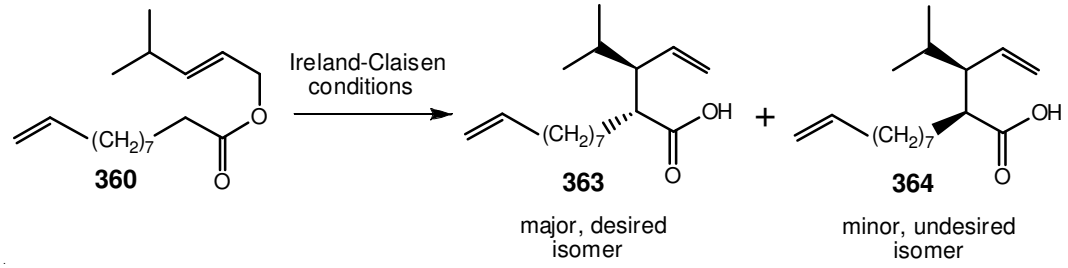


i) EDCI/DMAP 37%; ii) $SOCl_2$ 62%; iii) **284,** 2,6-lutidine 89% iv) Ireland-Claisen (See text)

Scheme 64

Synthesis was fairly straightforward (Scheme 64). The yield with EDCI (Scheme 64, step *i*) was again poor (37%), therefore the acid chloride **362** was prepared (step *ii*) by the method of Leydet and co-workers,[94] which was coupled with **284** (step *iii*) to give **360** in 89% yield.

2.2.4 Ireland-Claisen Rearrangement of Ester **360** to (*R**)-2-((*S**)-4-Methylpent-1-en-3-yl)undec-10-enoic acid **363**



Scheme 65

The general methodology of Viseux and Bouglas was followed, however the work-up was expedited by adsorption of the acid onto Ambersep-900-OH[95] resin. The author had previously used this technique[76] and this particular resin in the isolation of similar large, lipophilic acids, which form soapy emulsions (compare comments in 2.1.3.1) if extraction into aqueous base is attempted. This allowed quick and efficient separation of the acid **363** from starting material and neutral by-products. Adsorption (checked by TLC before and after resin treatment) appeared quantitative.

The acid was released from the resin with 4% formic acid in THF, followed by evaporation of solvent, and azeotropic removal of the formic acid with several changes of toluene. It should be noted that this method would be unsuitable in the presence of acid-sensitive protecting groups such as TIPS, TBDMS etc.

With respect to the actual rearrangement, Pennicott[91] recommended warming the reactions to 40-50°C to complete the rearrangement, his own experience[96] of similar reactions being that they did not reliably rearrange at ambient temperature.

Additionally, Bouglas recommended rapid addition of the base keeping the temperature low, and rapid addition of the TMSCl.[49]

The reaction was performed under a number of different conditions, the results of which are presented in Table 6 (overleaf and following page).

Ent	Scale g†	Eq Li HMDS	DMPU %††	ET (min)	ST (min)	RT (hrs)	RTmp (°C)	SC	Yield %	DR*	Comments
1	1.33	3	0	90	120	18	ambient	None	38	1:1.2	No selectivity expected
2	1.33	2	33	90	120	18	ambient	TMSTf	10	9:1	
3	1.33	2	31	75	180	18	ambient	TMSTf	11	8:1	
4	1.33	2	53	75	120	18	ambient	Et_3N**	23	5.2:1	
5	1.33	2	48	90	120	18 + 2	ambient then 40	Et_3N**	25	7:1	
6	1.33	4	30	60	10	2	50	None	52	5.3:1	Fast addition of TMSCl
7	1.33	4	47	60	10	3	50	None	37	6:1	Fast addition of TMSCl
8	2.66	4	30	60	10	3	50	None	53	6.5:1	Fast addition of TMSCl
9	3.99	4	30	60	10	3	50	None	53	6.1:1	Fast addition of TMSCl
10	6.0	4	33	60	10	3	50	None	67	7.2:1	Fast addition of TMSCl at –88°C
11	3	4	33	90	20	3	50	None	49	6.6:1	Enol soln frozen at -115°C, TMSCl soln (at -78°C) added, reaction allowed to warm to -78°C for silylation.
12	1.5	4	35	90	20	3	50	None	32	6.4:1	More dilute, enol soln frozen at -115°C, TMSCl soln (at -78°C) added, reaction allowed to warm to -78°C for silylation.
13	13.3	4	33	75	20	3	50	None	22	6.7:1	Larger scale, poor yield
14	20.0	4	33	75	20	3	50	None	27	7.7:1	Largest scale, poor yield
15	10.6	4	33	75	60	3	50	None	54	6.4:1	supercooled***
16	10.6	4	33	75	60	3	50	None	60	6.2:1	supercooled***
17	7.5	4	33	75	60	3	50	None	62	7.2:1	supercooled***

ET = Enolization Time ST = Silylation Time RT = Rearrangement Time
RTmp = Rearrangement Temperature SC = Silylation Catalyst

† Grams of starting material **360**
†† Approx. percentage by volume *i.e.* 100 x Vol DMPU/ (Vol DMPU + Vol THF)
* Ratio **363**:**364** Determined by NMR of methyl groups on isopropyl moiety (See 2.2.5)
** Pre-mixed with TMSCl and precipitate excluded as described.
*** See page 87 for details of supercooling procedure.

Table 6 (Part 1)

Ent	Scale g†	Eq Li HMDS	DMPU %††	ET (min)	ST (min)	RT (hrs)	RTmp (°C)	SC	Yield %	DR*	Comments
18	1.5	4	32	90	90	3	50	$TiCl_4$ 1.3%	27	6.6:1	Note $TiCl_4$ catalyst. Enol soln frozen at -115°, before TMSCl soln (at -78°) added
19	1.5	4	33	75	10	3	50	TMSTf	34	6.1:1	4.9 eq TMSTf alone used for silylation (no TMSCl used)
20	1.33	4	33	90	10	3	50	$SnCl_4$	trace	too dirty	$SnCl_4$ as catalyst,
21	2.1	1.2	0	90	60	3	50	None	0	N/A	No DMPU, 12-crown-4 used

See previous page for footnotes and abbreviations used in this table

Table 6 (Part 2)

It will be seen that, in the absence of DMPU (Table 6, Entry 1) the reaction was marginally diastereoselective in favour of the undesired isomer **364**, the product of the *E*-ketene silyl acetal formed from the *Z*-enolate. The reaction became markedly more diastereoselective (as hoped and expected) in the presence of 31-33% DMPU, although the yields dropped (Entries 2 & 3). The yields improved (Entries 4 & 5) when Et_3N rather than TMSTf was used a catalyst for the silylation, although to the detriment of the DR. When TMSTf alone (No 19) was used for silylation, the yield was also lower than that obtained with TMSCl under similar conditions.

Increasing the quantity of base (from 2 equivalents to 4 equivalents, Entries 6-20), warming the reaction to 50°C to complete rearrangement (Entries 6-21), and fast addition of TMSCl (no catalyst) increased the yield (Entries 6 & 8-10) to 52-67%. Increasing the proportion of DMPU to 47% (Entry 7) decreased the yield. Silylation was very exothermic, even with vigorous stirring it was difficult to keep the temperature below -60°C. Cooling to -88°C before addition (Entry 10) helped to control this. Freezing the reaction solid (Entry 11, approx -115°C), then adding the TMSCl as a pre-cooled (to -78°C) solution in THF/DMPU also controlled this exotherm, although slightly to the detriment of the DR and gave a reasonable yield (49%). Dilution (Entry 12) reduced the yield. Whilst the reaction had performed acceptably (Entry 10, 67% 7.2:1 DR) on a 6g scale, scaling–up proved detrimental (Entries 13, on 13g scale & 14, on 20g scale), halving the yield.

Use of catalytic quantities of the Lewis acids $SnCl_4$ and $TiCl_4$ were tried in the light of a publication by Koch and co-workers describing good DRs and yields,[95] however with the present substrate, using $TiCl_4$ (Entry 18) reduced the yield to 27% (the DR being unaffected), whilst using $SnCl_4$ (Entry 20) gave only traces of very dirty product. Use of the lithium-complexing crown ether 12-crown-4[98] in place of DMPU (Entry 21) gave no rearranged product.

The most reliable method appeared to be the 'supercooling' technique as used in Entries 15-17. The method is as follows:-
Upon completion of enolization, the reaction is cooled *rapidly* (taking care not to allow it to freeze solid) to between -90°C and -100°C, with continuous vigorous stirring. The reaction medium becomes very thick and syrupy, but the DMPU does *not* appear to crystallize out, as happens if the reaction is cooled *slowly* below about -85°C. Whether the reaction medium at this stage is actually supersaturated solution or a supercooled liquid is unknown.

When TMSCl is added under these conditions, it immediately freezes on the surface of the liquid, which can (and should) be kept stirring under the resultant 'raft' of frozen TMSCl. The temperature may now *carefully* be raised, still maintaining stirring. There is no apparent exotherm below –85°C, at which temperature a mild exotherm occurs, but the temperature may easily be kept below -70°C. With cessation of the exotherm the reaction, the reaction should be kept at -78°C for an hour, then warmed to ambient temperature and heated to 50°C as usual.

This technique gave yields of 54-62%, and DRs ranging between 6.4-7.2:1. Whilst far from satisfactory, the yield and DR were usable and appeared reproducible.

2.2.5 Determination of Diastereomeric Ratios of Ireland-Claisen Rearrangement Products **363** & **364**

Determination of the diastereomeric ratio **363:364** of the isomers **363** and **364** of the crude acid was carried out by integration of the NMR signals from the methyl groups of the isopropyl moiety. An example is shown in Figures 4 & 5.

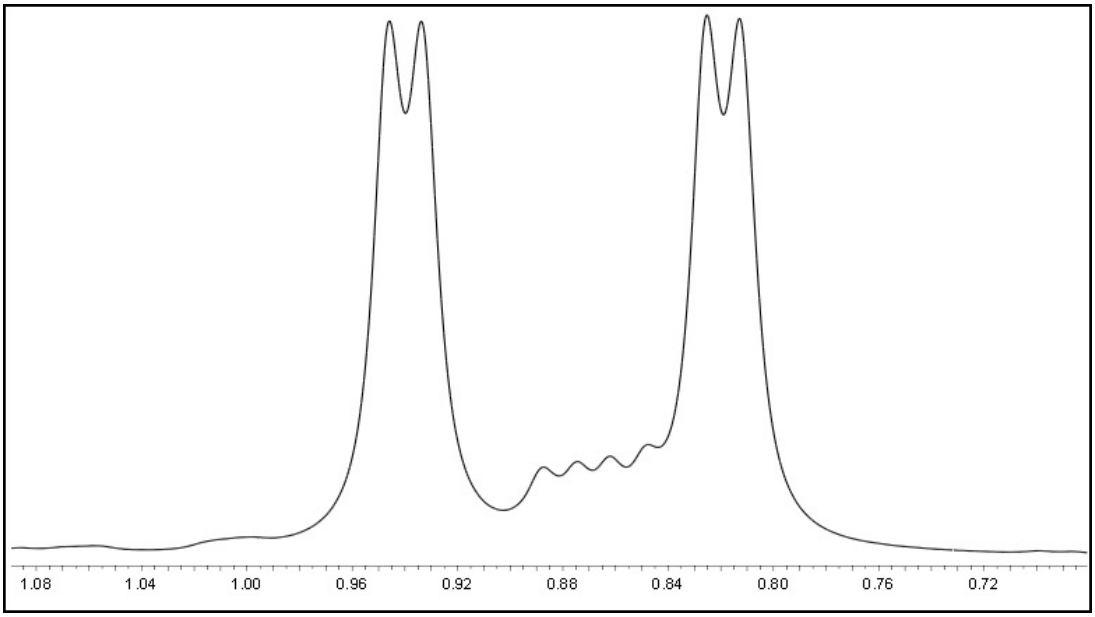


Figure 4

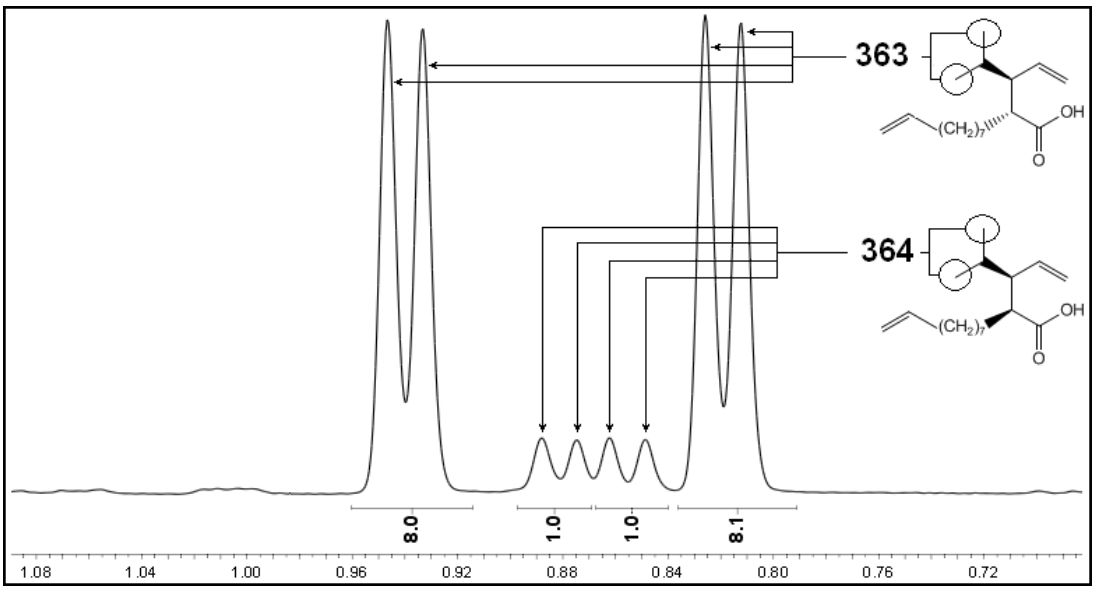


Figure 5

Figure 4 shows the spectrum of crude material (Entry 3 from Table 6), released from the resin and with the solvents removed under reduced pressure, to which spectrum only phase and baseline corrections have been applied.

Figure 5 shows the same spectrum to which Gaussian and exponential corrections have also been applied. With careful apodization, the signals due to **363** and **364** can be satisfactorily resolved, and integrated with reasonable confidence.[99] This allows the DR to be determined. In this case it is 8.1:1

The practicality of GC as a method for determination of DR was also investigated. A sample of the *same* batch of material (DR 8.1:1) of which the NMR spectrum is shown in Figures 4 & 5 was derivatized with BSTFA (compare 2.1.3.1, Scheme 56) to give the silyl esters **365** and **366** and subjected to GC. Figure 6 shows the full GC trace. Figure 7 shows the same trace, expanded and integrated, Figure 8 shows the mass spectra of the silyl esters.

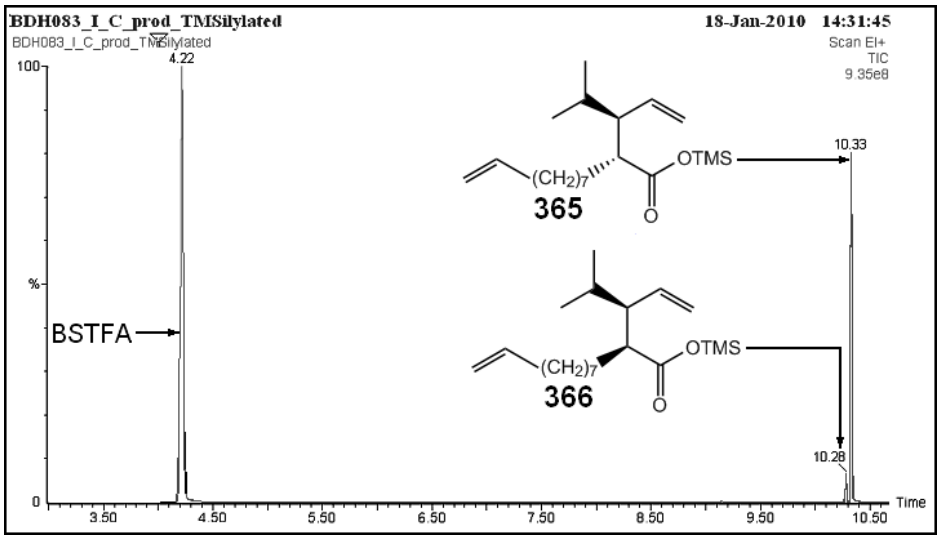


Figure 6

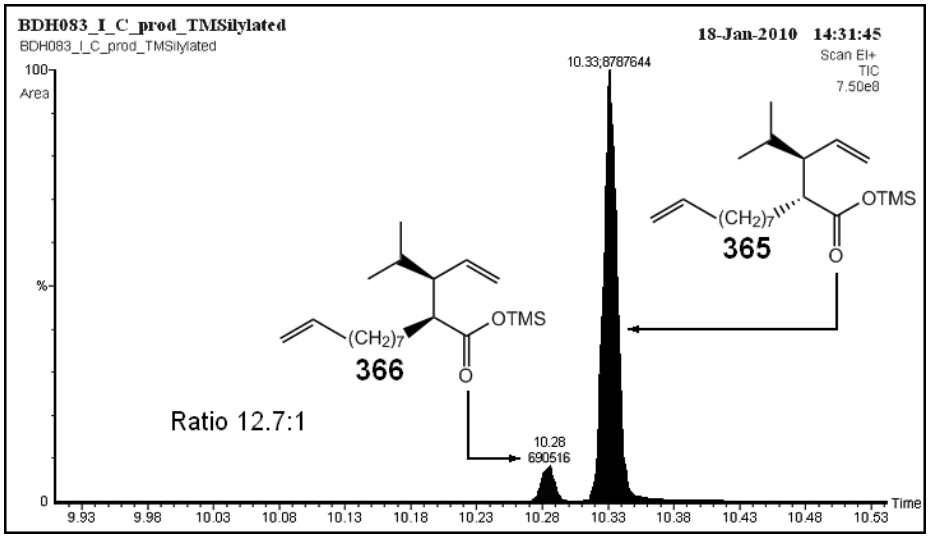


Figure 7

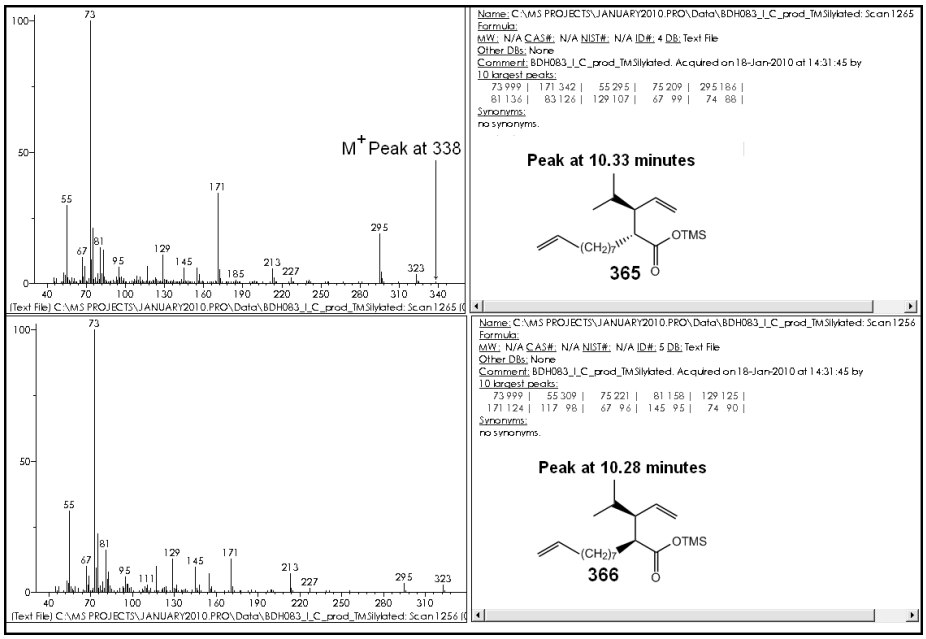


Figure 8

The mass spectra confirm the identity of the silyl esters. The spectra of the two isomers (see Figure 8) are practically identical (as would be expected), although only the spectrum of **365** shows the molecular ion (M^+ *m/e* 338), and even then this ion appears in low abundance, although this may be a concentration effect. The ratio of the integrals (Figure 8) of the silyl esters (identified by MS) are 12.7:1, and not the 8.1

determined by NMR. It should be noted that the integrated signals are TIC (total ion count), and, whilst the isomers are similar, and could reasonably be expected to ionize to a *similar* extent, there is no reason to suppose that they would ionize to an *identical* extent. In this case, treating the NMR integration as quantitative (*i.e.* assuming the 8.1:1 DR determined by NMR to be accurate), and assuming quantitative derivatization, it would appear that the major isomer derivative **365** ionizes (to a total ion count) 12.7/8.1 = 1.57 times greater than the minor isomer derivative **366**. This figure is approximate, and should be treated with caution. In order to obtain truly quantitative results it would be necessary to prepare a calibration curve of using samples of known composition and concentration.

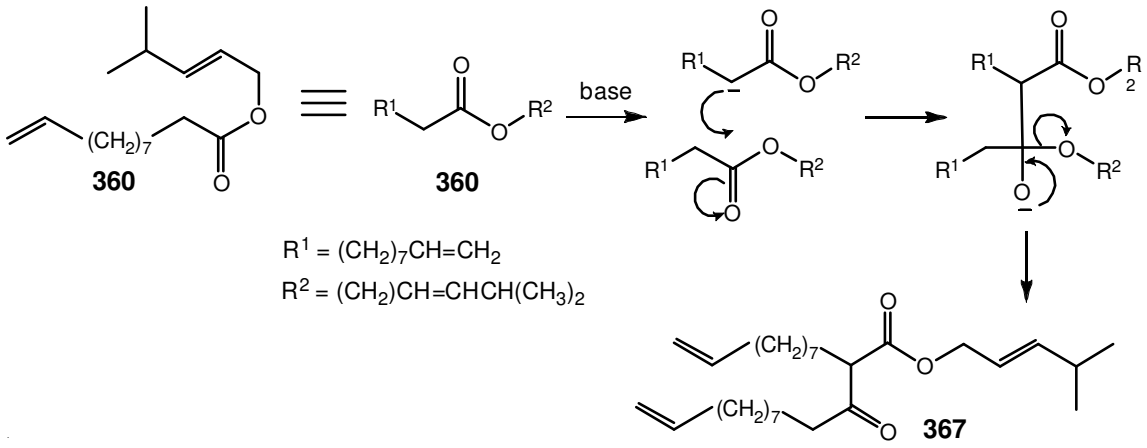
NMR turned out to be quick and practical, even on crude samples of mixtures of **363** and **364**, and (as a technique) it may be regarded as quantitative. The GC technique was considered to offer no advantage over NMR, and therefore was not further used or developed.

It should be stressed that neither technique actually *identifies* the stereochemistry. Both techniques merely determine the relative proportions of the isomers. Positive proof of the stereochemistry was obtained by bromolactonization (thereby locking the stereocentres into a rigid five membered ring) and an NOE study (see 2.3.2.1).

2.2.6 Separation of the Diastereomers **363** and **364** from the Ireland-Claisen Rearrangement

Separation of the isomers by column chromatography (MPLC) was not satisfactory. The compounds 'streaked' on TLC, and there was extensive co-elution with MPLC. Therefore the procedure became a repetitive, iterative process, consuming large amounts of time, silica and solvent.

This purification did, however, lead to the isolation (and, more usefully, the removal) of **367** from the mixed acids. This by-product results from the self-condensation (Claisen condensation) of **360**, which can occur if the temperature is allowed to rise during the enolization phase (Scheme 58). As a β-ketoester, the compound **367** is sufficiently acidic to be retained by the strongly basic Ambersep 900-OH resin.



Scheme 66

Given the poor separation, a better method was therefore sought. It was considered by the author that an anion exchange resin might be regarded (under some circumstances) as a hindered base, in that one side of the basic group is hindered by the plastic skeleton. It was also considered that the carboxyl group of **364** might be less hindered than that of **363** (see Figure 9, overleaf), and that this might be the basis of a viable separation of the isomers.

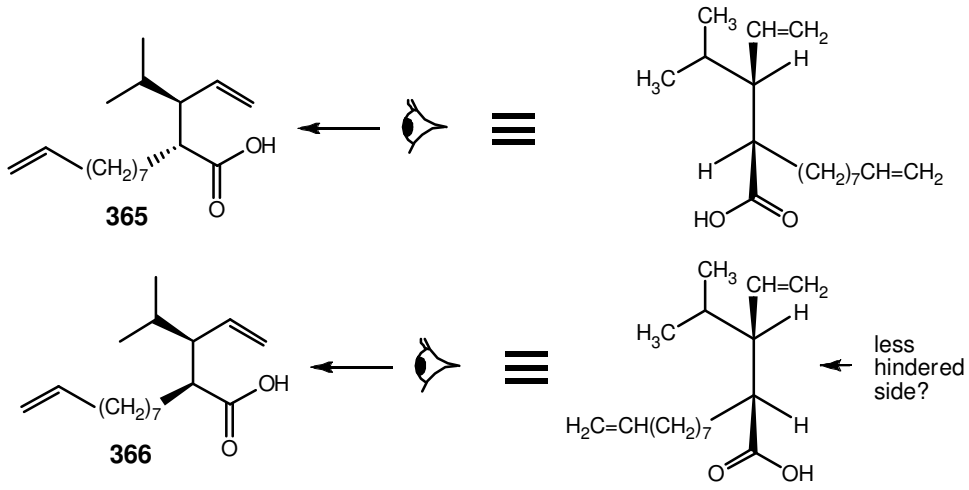


Figure 9

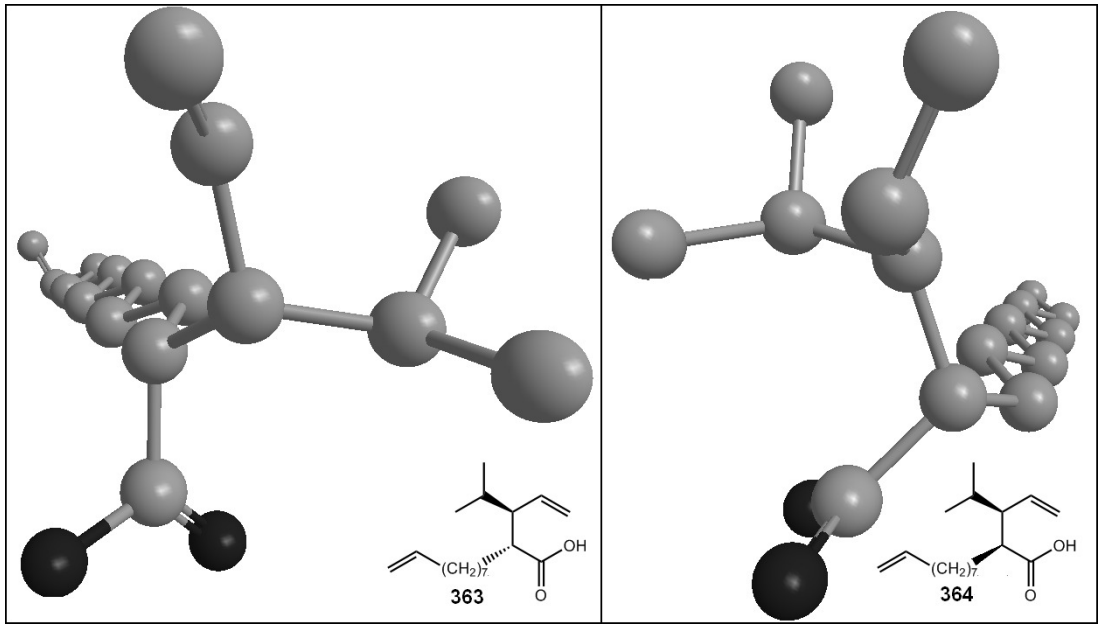


Figure 10

Molecular modelling of **363** and **364** (Figure 10) did not obviously support (or oppose) this view. The conformations shown are the calculated[100] minimum-energy conformations and neither appears (on subjective, visual inspection) to be noticeably more hindered than the other.

It should, however, be noted that the calculated minimum-energy conformation of a molecule in the gas phase does not necessarily bear any relationship to that of the molecule in solution, nor that of the same molecule in ionised form, nor of the molecule

ionised and bound to a resin. The possibility of selective adsorption was therefore investigated, the results being shown in Table 7

Ent	Resin	Ratio of Resin to Acid	Starting Mixture of acids **363:364**	Not retained by resin % (**363:364**)	Retained by resin % (**363:364**)	Comments
1	A26-OH * dehydr. in THF	2:1	5.61:1	53 (5.63:1)	47 (5.33:1)	High affinity for acid, little selectivity
2	Amberlyst A21 ** dehydr. in THF	1:1.5	2.47:1	96 (2.46:1)	4 (2.01:1)	Low affinity for acids, marginally preferential adsorption of **364**
3	IRA-67 *** dehydr. in diethyl ether	8:1	2.41:1	94 (2.42:1)	6 (1:>2)	Low affinity for acids, significantly preferential adsorption of **364** and other impurity BUT very dirty starting acid was used
4	IRA-67 dehydr. in diethyl ether	12:1	5.45:1	96 (5.5:1)	4 (3.5:1)	Low affinity for acids, marginally preferential adsorption **364** using higher DR starting material.
5	IRA-67 dehydr. in THF	12:1	5.39:1	94 (5.24:1)	6 (4.4:1)	Little affinity for acid, marginally preferential adsorption of **364** using higher DR starting material, possibly less selective than in diethyl ether

* A26-OH is a strongly basic quaternary amine hydroxide resin.[83]

** Amberlyst A21 is a weakly basic tertiary amine resin.[101]

*** IRA-67 is a weakly basic tertiary amine resin.[102]

Table 7

In all cases, the starting mixture of acids was dissolved in THF or diethyl ether, and stirred with a batch of resin. This is what is commonly termed ‘catch-and-release’, as opposed to a chromatographic technique. The adsorbed acids were then released with

10% formic acid in THF. As basic resins are liable to absorb carbon dioxide in storage, all samples were freshly regenerated (elution with aqueous HCl, then water, then aqueous KOH, then water) to remove this, then dried by elution with methanol, then THF or diethyl ether. The resins were selected simply on the basis of availability. The 'Ratio of Resin to Acid' column refers to the capacity of the resin. This figure is based upon milliequivalents per ml (of wet resin) or per gram (of dry resin), the capacity of a given resin being obtainable from the manufacturers data sheets.[83,101,102] The figure is approximate, all the resins swell in water, and shrink when dehydrated with THF, and shrink even more when dried with diethyl ether.

The strongly-basic (quaternary hydroxide) A26-OH resin has a good take-up of the acid (Entry 1). It will also be noticed that, despite the presence of 2 equivalents of base, only 47% of the acid was absorbed; adsorption was not quantitative. It will also be noticed that there is no evidence of selectivity. The second experiment (Entry 2) used A21 resin, a weaker (tertiary amine) resin, and an excess of mixed acid was used. It was hoped that this would lead to 'competitive' adsorption, but the overall take-up of acid was only 4%. However, the absorption was selective to some extent, the decreased DR of the released component indicated that a higher proportion of the undesired isomer **364** had been adsorbed. The third experiment (Entry 3) used IRA-67 (another weakly basic tertiary amine resin), only with the resin in excess. Take-up was again very poor (6%), but the selectivity was relatively high. However, both experiments (Entries 2 & 3) used very poor DR starting mixture. When repeated (Entry 4) using better material (DR 5.45:1) and a larger excess of the same resin (= more equivalents of base), whilst selectivity was evident, the effect was not spectacular. In the final experiment (Entry 5), the conditions were essentially the same (as in Entry 4), but THF was used as a solvent. This was tried as the resin shrinks less in THF, and it was considered that this might reduce its porosity and be the cause of some of the low uptake of acid. The difference in uptake was marginal (4%→6%) and the selectivity appeared somewhat reduced.

Separation by ion-exchange chromatography (adsorption onto A26-OH, and eluting with a very dilute solution of formic acid) was also attempted, without any noticeable separation being obtained.

Thus, it was determined that there was some degree of preferential adsorption of the undesired isomer **364** onto basic ion-exchange resins, in the case of weakly basic resins. Whether this is attributable to steric hindrance as originally proposed, or to

some other mechanism (or some combination of mechanisms) is unknown. Unfortunately the effect is very slight, and (given the low take-up of acid) the quantity of resin that would have been required for bulk purification would have been impractically large. Given the low degree of separation, this would have been another iterative process.

Overall, therefore, it was considered that this method offered no significant advantage over conventional chromatography; accordingly, the products of the various Ireland-Claisen rearrangements were combined, and separated by this latter method.

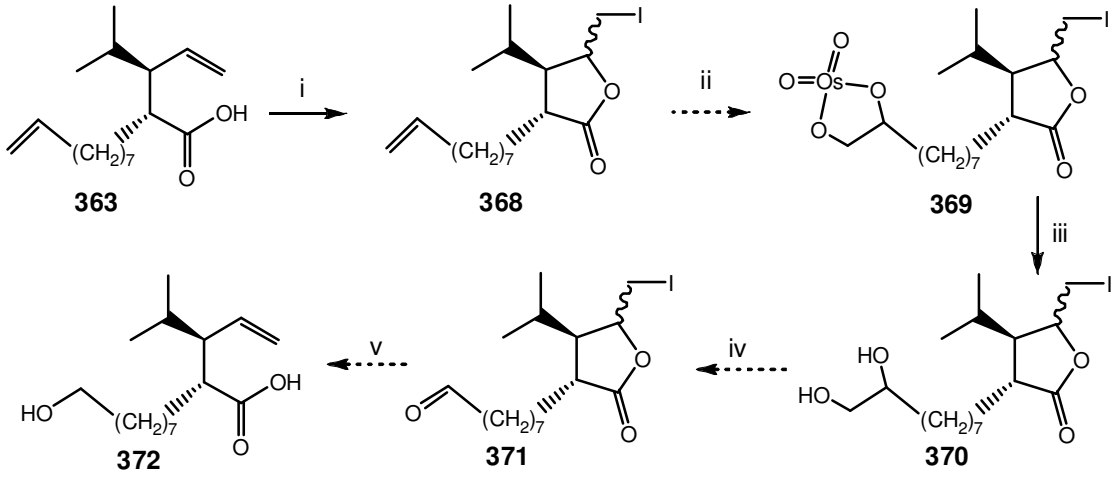
2.3 Differential Elaboration of the Terminal Double Bonds of **363**

The acid **363** has two terminal double bonds, and it was therefore necessary to differentiate between them, *i.e.* to protect the bond closest to the carboxyl, whilst turning the remote alkenyl group into a more useful functionality. Two approaches were taken to this procedure, iodolactonization and bromolactonization, to followed in either case by oxidative cleavage of the remote double bond.

2.3.1 Iodolactonization and Oxidative Cleavage

Iodolactonization (Scheme 60, step i), in addition to its protective function, 'locks' the two existing stereocentres into a rigid 5-membered ring. Viseux[48] separated the diastereomers in one example, and conducted an NOE study in order to prove the relative stereochemistry of the stereocentres formed in the Ireland-Claisen rearrangement, see 2.3.2.1.

It should be noted that iodolactonization may be 'reversed' (thereby recovering the γδ-unsaturated acid) by treatment with zinc and acetic acid,[103] as shown in Scheme 67, step v), in this case with the intention of simultaneously reducing the aldehyde function to an alcohol.[104]



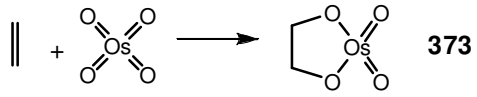
i) $I_2/H_2O/NaHCO_3$; 35-65 % ii) iii) OsO_4 [O] H_2O; iv) $NaIO_4$ v) Zn/AcOH

Scheme 67

Iodolactonization was performed according to the method of House and co-workers,[105] with iodine, water, and sodium bicarbonate in THF and is straightforward, giving a 65% yield of mixed diastereomers. Unfortunately the iodolactone is rather unstable, and deteriorates rapidly even in the freezer.

2.3.1.1 Osmylation and Cleavage of Olefins (Background)

The *cis*-hydroxylation of alkenes to give *cis*-diols using osmium tetroxide is a well-established reaction and has been extensively studied and reviewed.[106] The formation and structure of the cyclic osmate ester **373** are usually written as in Scheme 68, with the geometry of about the osmium unspecified, or else vaguely implied to be tetrahedral. This has the merit of convenience when describing mechanisms (and will be therefore be used, where appropriate, in the present work, *e.g.* Scheme 67, **369**) the actual situation is rather less clear-cut.



Scheme 68

The catalytic effect of osmium tetroxide was described by Hoffman[107,108] as early as 1912, who noted that it enabled chlorate solutions to attack unsaturated materials. This work was extended by Milas,[109,110] who used hydrogen peroxide with OsO_4 catalysis, now known as Milas' Reagent. Criegee[111,112] investigated the *stoichiometric* use of OsO_4, isolated various osmate esters and noted that the reaction was greatly accelerated by the presence of tertiary amines, especially pyridine. Criegee's work was revisited in 1974 by Griffith,[113] with the light of hindsight, and the benefit of spectroscopy and X-ray analysis, confirming the structures of the intermediates, as shown in Figure 11

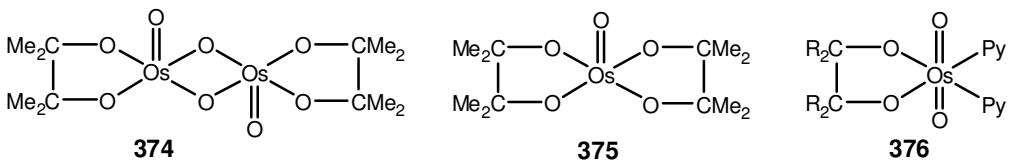
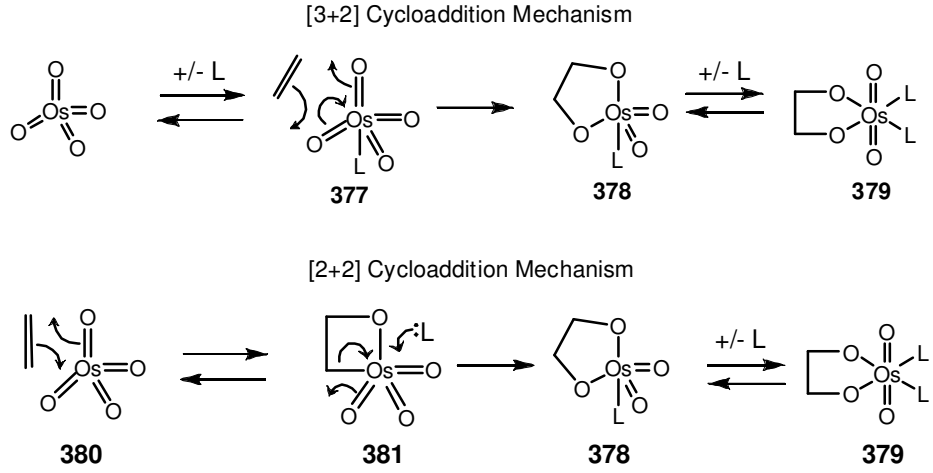


Figure 11

The 'monoester' *e.g.* **374**, the analogue of **373** derived from tetramethylethylene, was shown to be a bridged dimer, the osmium being held in a square-based pyramidal environment. Excess tetramethylethylene (or simple esterification of pinacol with OsO_4), gave the diester **375**. It should be noted that these are formed in the absence of tertiary amines. The compounds obtained in the presence of (*e.g.*) pyridine were shown to have the hexacoordinate structure **376**.

The mechanism of addition of the osmium tetroxide to the double bond (Scheme 63) has also been a matter of dispute. The two possible mechanisms[106,111] are shown in Scheme 69.



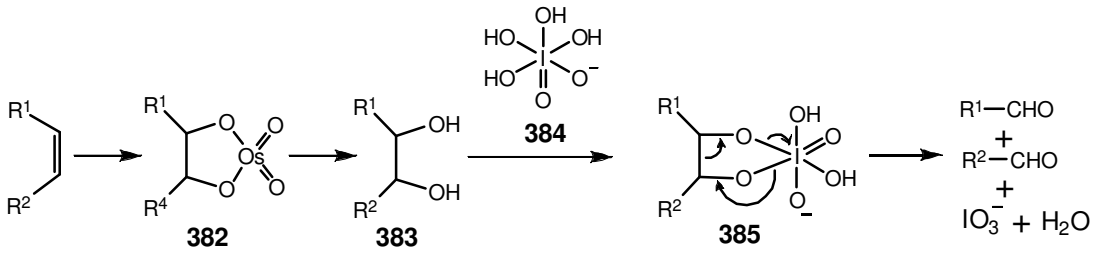
Scheme 69

The route involving a [3+2] cycloaddition **377** was favoured by Corey,[114] whilst the alternative mechanism of a [2+2] cycloaddition **380** followed by a ring-expansion **381** was proposed by Sharpless.[115] The controversy (for a summary see Reference 116) lasted 20 years until Sharpless published[117] evidence *in favour* of the [3+2] mechanism, which is currently the accepted route.

Regardless of the mechanism of its formation, a cyclic osmium (VI) ester may be cleaved either reductively or oxidatively. The former is only applicable when it is present in stoichiometric quantity. Many reducing agents may be used (sulfite, hydrogen sulfide, $LiAlH_4$)[106] giving reduced forms of osmium which may usually be removed by filtration. Oxidative cleavage (Os(VI)→Os (VIII)) regenerates OsO_4; this is the basis of its catalytic action. Many co-oxidants have been used besides chlorate and

hydrogen peroxide, eg *tert*-butyl hydroperoxide,[118] N-methylmorpholine-N-oxide (NMMO),[119] and sodium periodate.[120]

Sodium periodate with OsO_4 is known as the Lemieux-Johnson reagent, and differs slightly in application from the preceding examples (Scheme 70).[120] Initial osmylation (Scheme 70) by OsO_4, gives the cyclic osmate ester **382**, which is oxidatively cleaved by the periodate, in its capacity as co-oxidant to give the diol **383**.



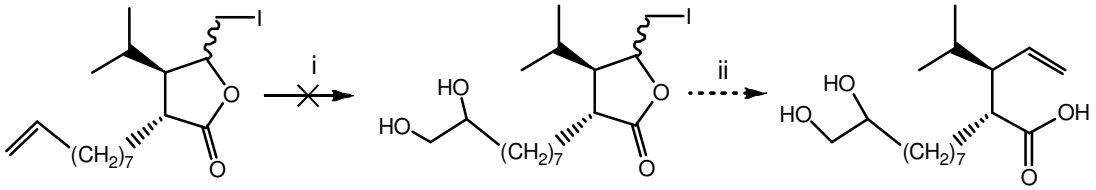
Scheme 70

However periodate ion (shown in hydrated form as **384** subsequently forms the cyclic periodate ester **385** and this (or possibly a dehydrated form)[121] decomposes to give two aldehydes and iodate ion.

2.3.1.2 Osmylation and Cleavage of Iodolactone **368**

Unfortunately, application of the periodate/OsO_4 system to the iodolactone **368** was unsuccessful under a variety conditions. Yields of 0-29% of mixed acidic materials were isolated. NMR indicated that the terminal methylene group appeared to have been removed, and the spectra obtained were approximately consistent with mixtures containing **372**.

The periodate was therefore replaced with N-methylmorpholine-N-oxide, a co-oxidant which does not cleave diols, with the intention of preparing the diol-acid **386**. This also was unsuccessful (Scheme 71).



368 **370** **386**

i) OsO_4 /NMMO ii) Zn/AcOH

Scheme 71

The main problem was the instability of the iodolactone itself, even when freshly prepared and used as a solution immediately. In addition, the persistency of the osmium during work-up was troublesome. Osmium is a particularly undesirable impurity in the reduction stage. Zinc and acetic acid generates hydrogen, and Zn(0) will reduce any remaining osmium compounds to finely divided osmium, which is a perfectly good hydrogenation catalyst,[122] although it is (understandably) rather seldom used. Whether this was a significant contributing factor to the poor results is unknown.

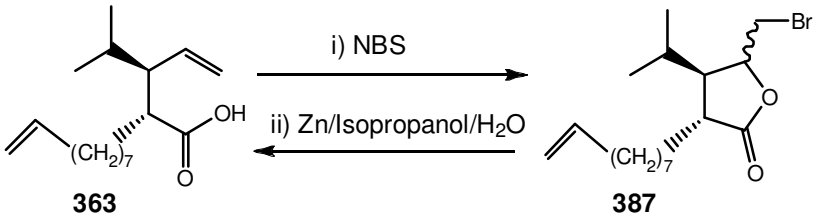
The obvious alternative to osmylation was ozonolysis, however this presented the possibility of oxidation of the iodine, and formation of hypervalent iodine species. Hypervalent iodine compounds have found extensive use,[123] but have a reputation for being explosive. Opinion seems divided, especially with regard to the widely used 2-iodoxy benzoic acid (IBX), the precursor to Dess-Martin periodinane, although Dess and Martin[124] themselves attribute most of the problems to contamination with bromate from inadequate purification. It was considered that the preparation of an ozonide (almost certainly explosive) which might also contain hypervalent iodine species, in the presence of ozone would be unacceptably hazardous. The iodolactone route was therefore abandoned.

2.3.2 Bromolactonization and Oxidative Cleavage

The strategy behind the bromolactonization was essentially the same as the previous section, however use of a bromolactone would allow the options of osmylation or ozonolysis. The first requirement was therefore to locate an effective bromolactonization technique, and an equally effective technique for regeneration of the unsaturated acid.

2.3.2.1 Bromolactonization and Regeneration of **363**

Bromolactonizations seem to have attracted less attention than iodolactonizations, as have their 'reversals'. Ohfune and co-workers,[125] had published a method using NBS, which, after modification and optimization, gave acceptable yields (48-71%) of **387** (Scheme 72, step *i*). A 'reverse reaction' due to Hanessian,[126] using zinc powder in damp isopropanol was also found, and tested (step *ii*).



Scheme 72

The bromolactone **387** proved much more stable than the iodolactone **368**. The bromolactone **387** is a mixture of **388** and **389**, which were separable by chromatography (Figure 12).

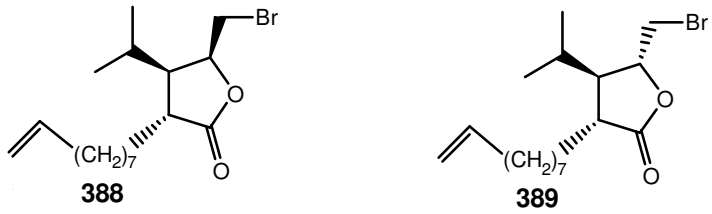


Figure 12

A sample of each of these isomers was accordingly subjected to an NOE study in order to prove the relative stereochemistry of the isopropyl and side-chain, as had been performed by Viseux on an iodolactone, as mentioned in 2.3.1. The details are given in the Experimental section. The assigned stereochemistry was proven to be correct.

2.3.2.2 Osmylation and Cleavage of Bromolactone **387**

Given the problems previously encountered with osmium tetroxide, an alternative method for its use was sought. A method due to Yang and co-workers[127] was found where OsO_4 was immobilized upon XAD4 resin, and used in that form.

XAD4 is *not* an ion exchange resin, but an adsorption resin relying upon its large surface area for its efficacy. In this respect, it may (rather crudely) be regarded as a plastic version of activated charcoal. The manufacturer's data sheet[128] portrays it (Figure 12) as a styrene polymer, with divinylbenzene providing the cross-linking **390**.

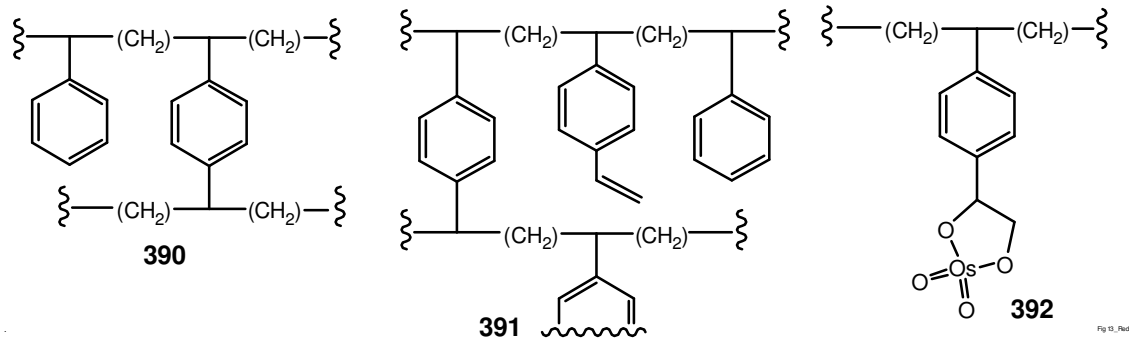


Figure 13

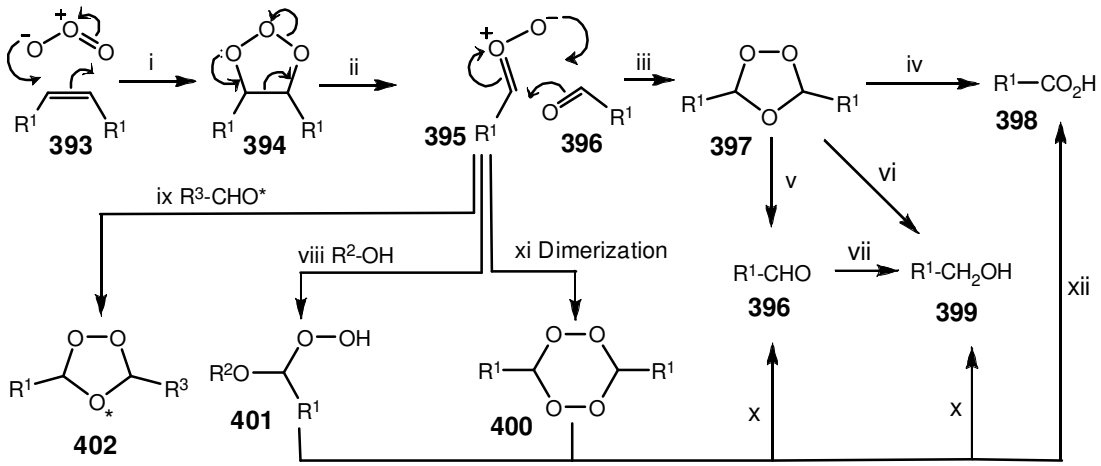
The material is, however, described by Darling and co-workers in a paper discussing chemical modifications of the resin as *'a styrenic copolymer of meta- and para-isomers of divinylbenzene (80-85 wt%) and ethylvinylbenzene (15-20 wt%)'*.[129] Manufacturers (quite understandably) are generally unwilling to disclose the exact nature of proprietary materials, preferring to sell them as 'black boxes' *i.e.* as products with specific properties. Regardless, in a polymerized mixture containing divinylbenzene, there will be 'residual' vinyl groups (*i.e.* where only one vinyl group on an incorporated molecule of divinylbenzene has participated in polymerization) as in **391**, and these groups may be modified if desired. In the case under consideration the presumption is that the osmium is retained upon the resin as cyclic osmate ester moieties **392** formed

from the residual vinyl groups. This, according to Yang and co-workers[127] gives a catalyst which is non-volatile, filterable, air-stable, re-usable, and does not leach out osmium.

Unfortunately, when applied to **387**, with periodate (diol-cleaving conditions) or with *t*-butyl hydroperoxide or NMMO (diol-preparing conditions) complex mixtures and/or decomposition resulted. Osmylation was therefore abandoned.

2.3.2.3 Ozonolysis (Background)

Ozonolysis of double bonds is another well-established reaction extensively studied by Criegee.[130] The mechanism as currently understood is shown in Scheme 73.



Scheme 73

The sequence begins (Scheme 73, step *i*) with a [3+2] cycloaddition, giving the 1,2,3 trioxolane structure **394**, also known as the 'molozonide' or 'primary ozonide'. This is a highly unstable structure, which undergoes a cycloreversal (step *ii*) to the aldehyde **396** and the key intermediate **395**, the carbonyl oxide, or 'Criegee intermediate.' This is a very reactive species, which immediately undergoes (step *iii*) another [3+2] cycloaddition to give the 1,2,4 trioxolane **397** usually referred to simply as 'the ozonide'. Ozonides of the general structure **397** may actually be isolated, however this is inadvisable if at all possible, as they are not-infrequently explosive. More usually they are worked up without isolation. The ozonide **397** may be worked up either oxidatively (step *iv*) (*e.g.* with hydrogen peroxide[131]) to give the carboxylic acids or (more

commonly) reductively (step *v, vi,* or *v* followed by *vii*) to give aldehydes and/or ketones **396,** or (with more vigorous reduction) alcohols **399** as desired.

The evidence for the mechanism (summarized by Criegee[130]) is extensive. The carbonyl oxides **395** are too short-lived to be observed directly, however, products of their reactions may be isolated.[132] They may dimerize (step *viii*) to give 1,2,4,5-tetraoxanes **400**. If the ozonolysis is conducted (step *viii*) in the presence of an alcohol R^2-OH, hemi-peroxy-acetals **401** may be obtained. If the reaction is conducted (step *ix*) in the presence of another aldehyde (R^3-CHO*) the 'crossed' ozonide **402** will be obtained in addition to **397**. The oxygen of (R^3-CHO*) is shown as labeled. In such O^{18} labelling experiments, the labeled oxygen ends up exclusively as the ether-bridge. Finally, it should be noted that **393** is symmetrical. In an unsymmetrical case ($R^1CH=CHR^4$), four products are likely to be obtained in the presence of R^3-CHO, as two possible carbonyl oxides may be formed from the molozonide. It should be stressed that there are many other reactions of carbonyl oxides, reviewed in Reference 129.

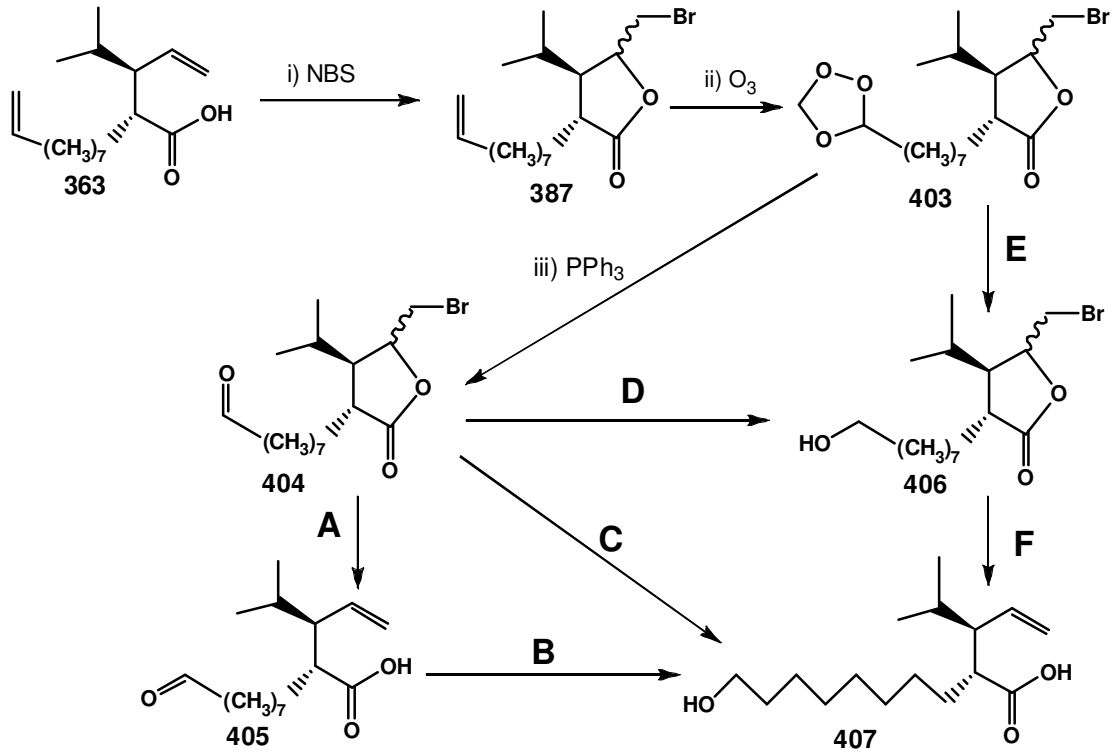
From a practical point of view the formation of **400** or **401** in addition to **397** is not usually a problem, both can be as readily reduced (step *x*) to carbonyl compounds **396** or alcohols **399** as can **397**. Similarly they can be oxidized (step *xii*) to carboxylic acids.

Reductive work-up is the most common. Modern (and safest) practice is to work up the ozonide without isolation (*i.e.* still in the solution in which it was made) and, given ozonolyses are typically conducted at -78°C, to perform the reduction at low temperature. Many reducing agents have been used, which is unsurprising, given that just about *any* reducing agent will reduce peroxides. Zinc, sodium bisulfite, catalytic hydrogenation, potassium ferrocyanide[133] have all been used, as have lithium aluminium hydride,[134] and trivalent phosphorus compounds.[135] Modern practice is to use dimethyl sulfide, trimethyl phosphite, or triphenyphosphine. Dimethyl sulfide and trimethyl phosphite have the advantage that the oxidation products (respectively: DMSO and $O=P(OMe)_3$) are water soluble. Also, both possess the questionable advantage of volatility: whilst both may be readily removed under reduced pressure, they both have utterly intolerable odours. Triphenylphosphine is generally reckoned to be the most reliable reductant, and therefore the safest,[91] its only real disadvantage being the necessity of removal of the triphenylphosphine oxide. Thus, the safest and best practice is to conduct the ozonolysis at -78°C, add an excess of triphenylphosphine at the end of the reaction (whilst still at -78°C) and then allow the

reaction to warm up. Further details (especially safety precautions) are given in the Experimental section.

2.3.2.4 Ozonolysis, Reduction and Regeneration of Unsaturated Acids from Bromolactone **387**

The approach to the hydroxy-acid **407** is presented in Scheme 74, which requires some explanation. There are several possible routes through this scheme. The preparation (Scheme 74, step *i*) of the bromolactone **387**, and its reversal are unambiguous and have already been described. The actual ozonolysis (step *ii*) to give the ozonide **403** and the reduction (with triphenylphosphine) are similarly unambiguous. Other routes from **403** and **404** are marked A to F.



Scheme 74

At the commencement of this investigation, and with the benefit of hindsight, it was assumed that in order to open the bromolactone to give a 4,5-unsaturated acid, depending upon the route taken, either A or C needed to be Zn/IPA/H_2O. By implication this would apply also to F, but the route EF was not initially considered. It was hoped that the Zn/IPA/H_2O, in addition to opening the bromolactone would also reduce the

aldehyde function, thus route C would give **407**. In the event of the aldehyde function not being reduced, it was assumed that the aldehyde **405** would be obtained. This would need to be reduced (route B) to **407** as soon as possible, given that aliphatic aldehydes oxidize readily in air. The method chosen for isolation of the final product following the Zn/IPA reduction was to remove unreacted zinc by filtration, remove the solvent, to acidify the residue, extract the organics, and then adsorb the acid portion onto Ambersep-900-OH (as had proved successful with the Ireland-Claisen rearrangements), then releasing with formic acid.

Accordingly, ozonolysis was performed, details of the first three ozonolyses (that being all that the available stock of starting material permitted) being presented in Table 8.

Entry	Details	Results		Entry	Details	Results
1	0.12g i) Ozone ii) PPh_3 iii) Zn/IPA/H_2O iv) Ambersep 900-OH work-up	65% ~60 mg of crude aldehyde-acid	→	4	$NaBH_4$/MeOH	10% <4 mg possible 407
2	0.12g i) Ozone ii) PPh_3 iii) Zn/IPA/H_2O iv) Ambersep 900-OH work-up	~70 mg 90% very crude aldehyde-acid	→	5	$NaBH_4$/ THF	~40 mg Unidentified No C<u>H</u>O but No C<u>H_2</u>OH either
3	0.12g i) Ozone ii) PPh_3 iii) Zn/IPA/H_2O iv) Ambersep 900-OH work-up	Yield N/D used direct for reduction	→	6	Sodium Dithionite/ Dioxane/ $NaHCO_3$	Complex mixture

Table 8

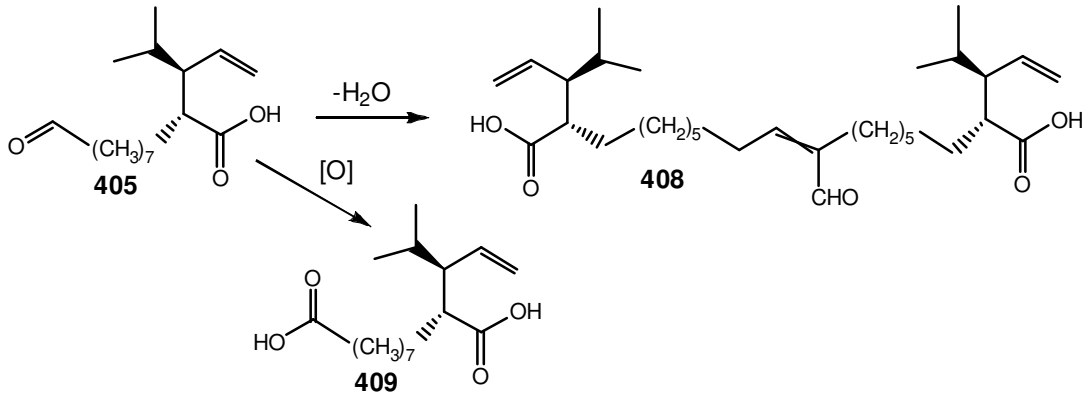
The first reaction (Entry 1) produced what appeared (from the NMR) to be very crude aldehyde; therefore full characterization was not attempted, but the compound was immediately reduced (Entry 4) with $NaBH_4$/Methanol. A trace of impure (probable) **407** was obtained. A repeat ozonolysis (Entry 2) gave a still less satisfactory sample of aldehyde, a (milder) reduction (Entry 5) with $NaBH_4$/THF gave unidentified material. The product of the final (Entry 3) ozonolysis was immediately reduced with sodium dithionite/dioxane/$NaHCO_3$ [136] but gave a complex mixture.

Whilst further **363** was prepared, a mild, reliable reduction of aldehydes to alcohols was sought. A method by Justicia and co-workers[137] using manganese powder in damp THF

in the presence of 2,4,6-collidine hydrochloride (to activate the metal surface) was found, and investigated using heptanal as a convenient model. It was found that this reaction also worked in isopropanol, although it had a tendency to 'stick' and need the addition of fresh manganese, presumably due to surface inactivation. Sonication appeared to prevent this. The rationale for the change of solvent was that it could be used in conjunction with the zinc, this being route DF in Scheme 74. The system was tried on a sample of **387**, in order to ascertain whether it would also effect the 'reversal' (Scheme 72, step *ii*), however this did not occur. Applied to the real system, a trace of (probably) **407** was tentatively identified. A second run yielded a mixture of at least 3 products, and whilst none of them were positively identified, none of them were **407**.

The route EF was also attempted, using borane/dimethyl sulfide complex, which is claimed to reduce ozonides directly to alcohols.[138] In this case only highly polar material devoid of alkenyl protons by NMR was obtained.

The route AB was then retried, using zinc borohydride, to effect step B. Zinc borohydride is a mild reducing agent extensively investigated by Ranu and co-workers[139] and reported by this group as being suitable for aldehyde to alcohol reductions.[140] However, a sample of the putative **405** was examined whilst the bulk of it was under reduction. It turned out to be a mixture, from which the dimer **408**, the result of the aldol-type self-condensation (Scheme 75) of the aldehyde **407**, was isolated by chromatography.



Scheme 75

The spectra of the original (known to be impure) sample of **405** were re-examined in the light of hindsight. The MS showed the (expected) presence of the diacid **409**, due to oxidation by air, plus the dimer **408**. The sample (by NMR) contained approximately

64% of **409**, 33% of **405** and 3% of **408.** Given that the aldol condensation is base-catalysed, it was considered that over-prolonged heating in Zn/IPA/H_2O (basic due to presence of ZnO and $Zn(OH)_2$ was best avoided. However it would appear that this dimerization also takes place in essentially neutral conditions *i.e.* $CDCl_3$ at ambient temperature. Figure 14 shows the original proton spectrum (C**H**O region of spectrum only) of the crude material, along with one of taken of the same sample taken 4 days later. It will be seen that the relative proportion of dimer had approximately doubled in that time.

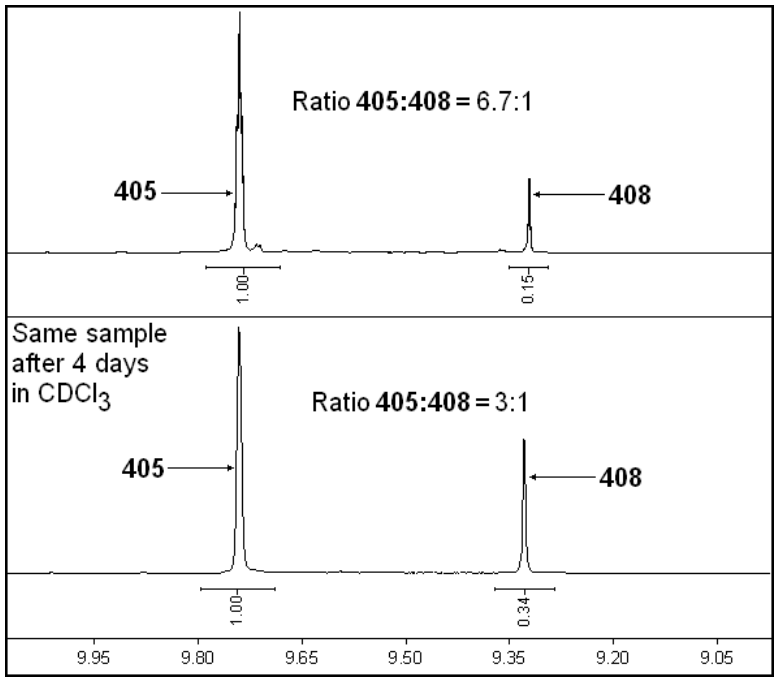
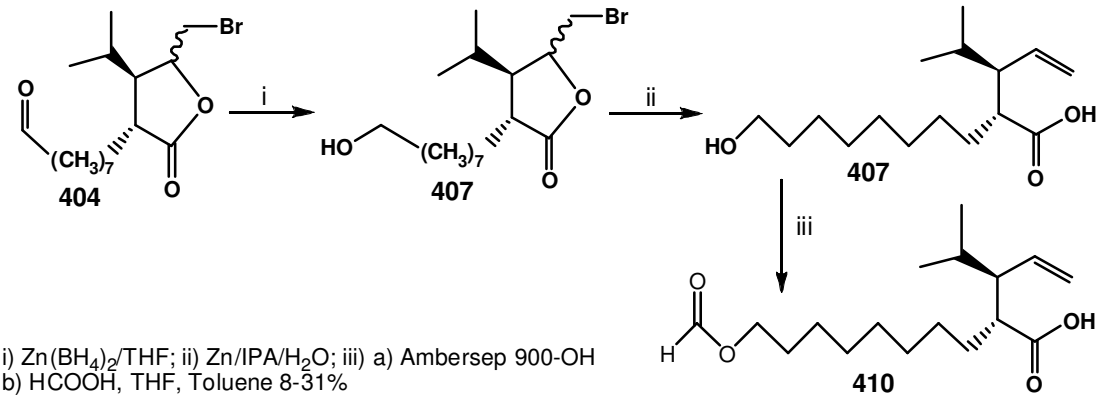


Figure 14

Accordingly (referring back to Scheme 74) the route DF was retried using zinc borohydride to reduce the aldehyde function of **404** before the Zn/IPA/H_2O treatment as shown in Scheme 76. The result was somewhat unexpected, the isolated product **410** being the O-formyl derivative of **407**.

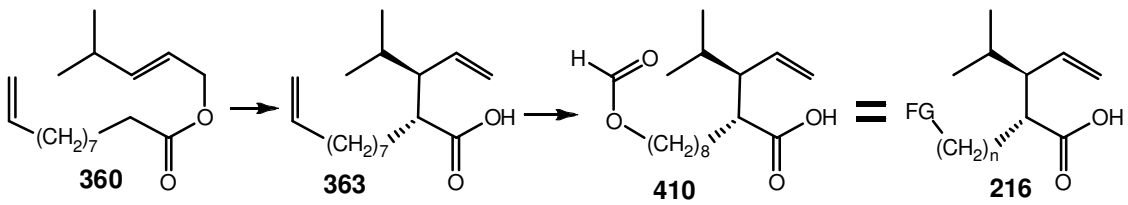


i) $Zn(BH_4)_2$/THF; ii) Zn/IPA/H_2O; iii) a) Ambersep 900-OH b) HCOOH, THF, Toluene 8-31%

Scheme 76

It is presumed that the hydroxy acid **407** was actually formed, and 'caught' upon the basic resin. This acid was released with a large excess of formic acid in THF, purified by chromatography with 1% formic acid in dichloromethane as eluent, and the formic acid removed from the product under reduced pressure with several charges of toluene, as formic acid forms an azeotrope with toluene.[141] However toluene also forms an azeotrope with water,[141] thus the isolation procedure could equally well be viewed as 'heating with formic acid with azeotropic removal of water'. These are classic esterification conditions, and formylation is (in retrospect) unsurprising. The reaction was performed twice. The yields were poor, 8% (with recovery of some **363**, from incomplete ozonolysis) and 31% respectively, however there is no reason to suppose this could not be improved upon.

Thus the feasibility of preparing an intermediate of the general structure **216**, with a useful FG at the remote end of the chain, from the ester **360** had been demonstrated (see Scheme 74). Whilst the Ireland-Claisen itself gave only moderate yields and DRs, the acid **363** is chemically very robust, and will tolerate extensive purification without deterioration, unlike a material with a more delicate protecting group.



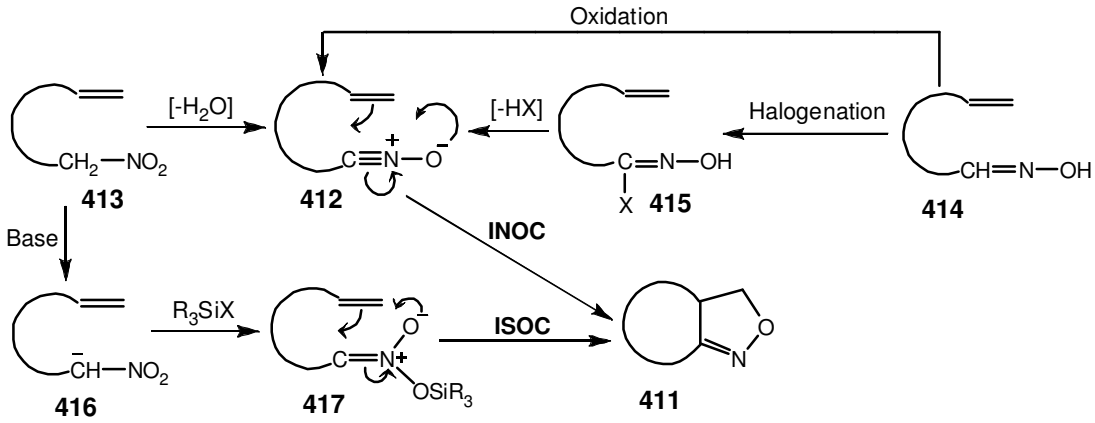
Scheme 77

2.4 Incorporation of Nitrogen

At this point, attention was shifted to methods of installing the nitrogen function into the molecule in a synthetically useful manner.

2.4.1 The α-Nitroketone and INOC Approach

The INOC (Intramolecular Nitrile Oxide Cycloaddition, or Intramolecular Nitrile Oxide Olefin Cycloaddition)[142] and the closely-related ISOC (Intramolecular Silyl Nitronate Olefin Cycloaddition),[143] shown in generic form in Scheme 78, were considered to be worth investigation.



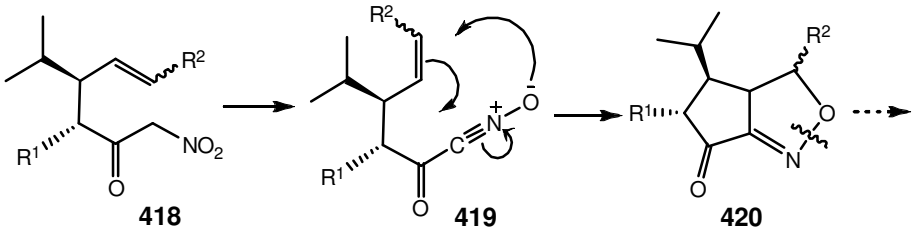
Scheme 78

In the first case (for INOC), starting from a nitro compound **413**, it is necessary to dehydrate the substrate, which may be done with phenyl isocyanate (or many other reagents),[143] to form the nitrile oxide **412**, which subsequently undergoes the INOC cyclization to **411**. If starting from an aldoxime **414** it may be halogenated to a hydroximoyl halide **415**, and immediately dehydro-halogenated to give the nitrile oxide **412**. Alternatively, **414** may be oxidized in some other manner.

In the second case (for ISOC), the nitroalkane **413** may be deprotonated to give **416** and silylated (*e.g.* by Et_3N and TMSCl) to give the silyl nitronate **417**, which cyclizes to give the isoxazoline **411**. Isoxazolines may be reduced (cleaving the N-O bond) to the

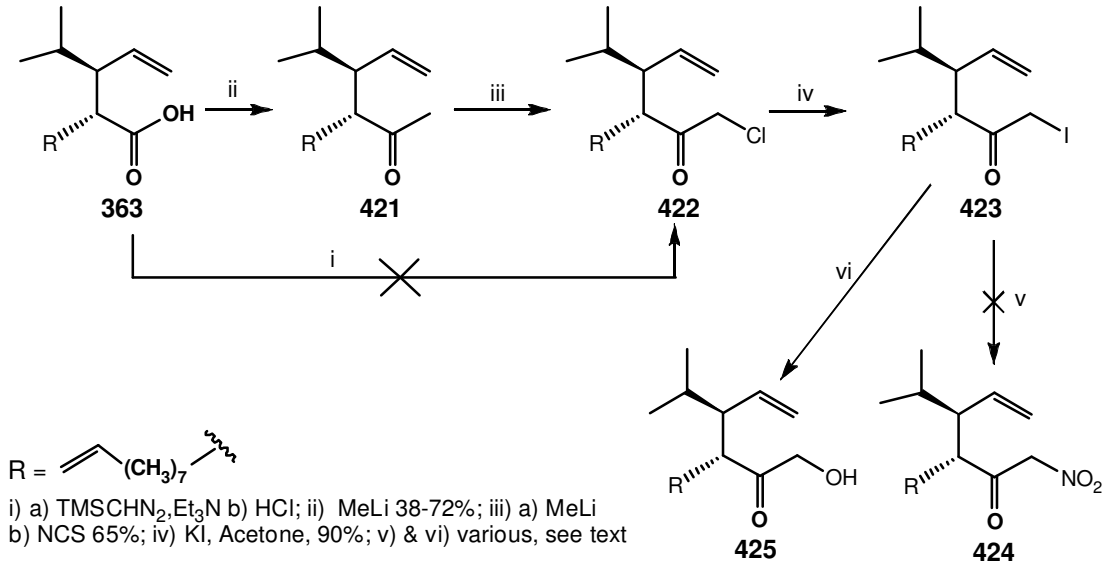
open chain γ-nitrogen-containing compounds, *i.e.* γ-amino alcohols,[144] or, with milder reduction (*e.g.* Raney nickel[145]) to γ-hydroxy imines.

Applied to the system under consideration, this approach is summarized in Scheme 79



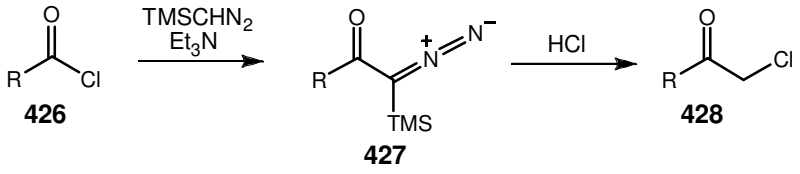
Scheme 79

Reducing to practice, it was decided to prepare the nitroketone **424**, the proposed routes being shown in Scheme 80



Scheme 80

Direct preparation (step *i*) of the chloroketone **422** was attempted *via* a variation on the Nierenstein reaction (Scheme 80). In this variation,[146] the diazomethane of the classical version[147] is replaced with (safer and easier to handle) trimethyl silyldiazomethane, and the resultant TMS-diazoketone **427** decomposed with ethereal HCl (Scheme 81).



Scheme 81

Applied to the acid **363**, no trace of **422** could be detected (Scheme 80, step *i*). There was no obvious reason for this failure, other than that the carboxyl group in **363** is very hindered.

The route *via* the ketone **421** was therefore investigated (Scheme 80, steps *ii* and *iii*). Preparation of ketones from lithium carboxylates is a well established reaction,[148] and had previously been used upon similar substrates.[48] The reaction gave acceptable yields, although it is sensitive to the quality of the MeLi. In cases where the yield was low, some of the starting material could be recovered, moreover **363** was more susceptible to attack by the MeLi than **364**, resulting in an improved DR in the product (see Table 9).

Starting acid **363**	Ketone **421**	Recovered Acid **363**
Yield N/A (100%)	Yield 72%	Yield 11%
DR 8.4:1	DR 12.8:1	DR 3.7:1

Table 9

Modelling of the carboxylate anions (Figure 15, overleaf, energy-minimized structures)[100] suggested that approach by an incoming nucleophile to one side of the carboxylate moiety in **364** would be hindered by the isopropyl group, whilst in **363** both sides would be fairly accessible to attack. Regardless of the exact origin of the effect, the improvement in DR was welcome.

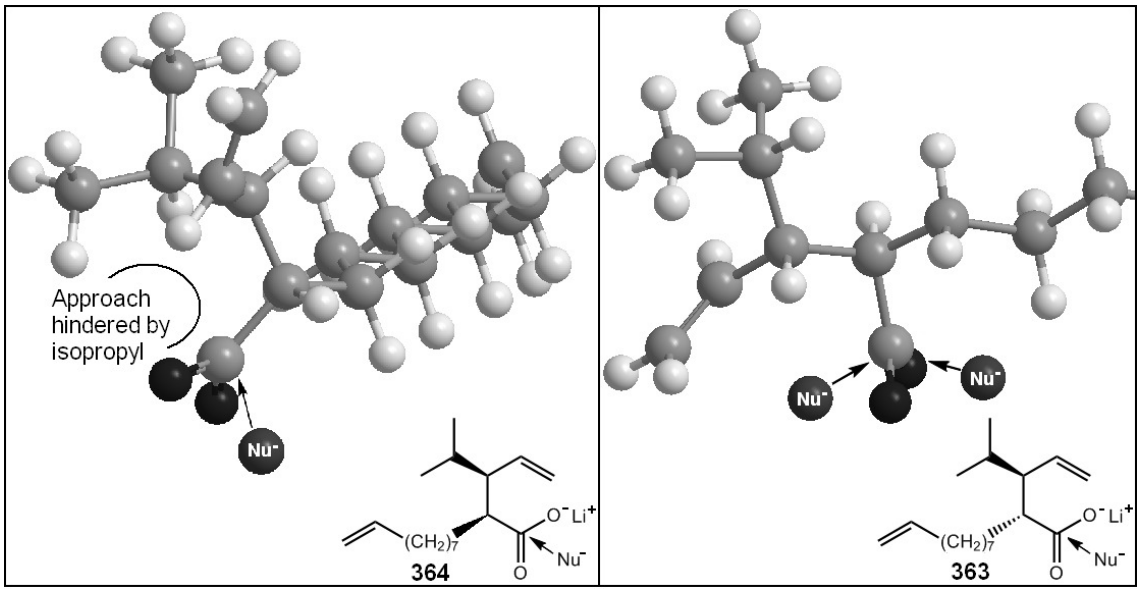


Figure 15

Conversion to the chloroketone[48] was straightforward (although the requirement for using fresh MeLi, and for the NCS to be freshly recrystallized from benzene should be stressed), as was the conversion to the iodide under Finkelstein[31,149] conditions, ready for conversion to the nitroketone **424**, see Table 10

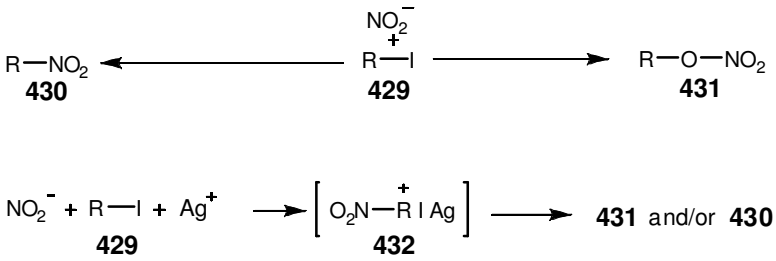
Entry	Reagent	Results
1	IRA-900-NO_2	Starting material consumed (X2)
2	$AgNO_2/Et_2O$	No reaction, starting material remained
3	$AgNO_2/Et_2O$/Sand	No reaction, starting material remained
4	$NaNO_2$/Phloroglucinol/DMF	Hydroxyketone **425** 13% (2mg)
5	$NaNO_2$/Phloroglucinol/DMSO	Hydroxyketone **425** Yield N/D
6	$NaNO_2$/Urea/DMF	Hydroxyketone **425** Yield N/D

Table 10

All of the above were tried on small scale, <20 mg. Exchange of iodine for NO_2 was first attempted (Entry 1) using IRA-900-NO_2. This material is an anion-exchange resin in nitrite form, and is commercially available as such.[150] The reaction was attempted twice in benzene.This published metho[151] had previously been used successfully within the Parsons group,[152] however, in the present case, whilst GC indicated consumption of starting material, no product was observed.

It was considered possible that the product may have been sufficiently acidic to be adsorbed by the resin, however, nothing containing a nitro group (examined by IR) could be recovered upon acidification of the resin.

Reaction of **423** with silver nitrite (the Victor Meyer reaction)[153] was tried (Entries 2 & 3) next. Nitrite ion may react with an alkyl halide **429** to give either a nitro-compound **430** or a nitrite ester **431** dependent upon the conditions (Scheme 82) .



Scheme 82

The generally accepted explanation is that the silver salt forms an ion-pair transition state **432**,[154] which may break up to give either **430** or **431** and the more closely the situation resembles SN_1 (*e.g.* with a tertiary halide) the more the nitrite ester is favoured, whilst conditions favouring SN_2 (*e.g.* with primary halides) favour production of nitro compounds.[155]

Consequently, primary halides can give good yields of nitro-alkanes, whilst tertiary ones do not. The situation is complicated by the fact that the reaction is occurring at a surface ($AgNO_2$ being insoluble in ether) and that the transition state is solvated, Practically, a mixture of nitrite ester and nitro compound is usually obtained.

Referring back to Table 10, Entry 2, stirring **423** with $AgNO_2$ (absolutely fresh, in the dark, under N_2) gave no reaction. In Entry 3, a modified procedure due to Lucas[156] was used, clean sand being added to act as an abrasive during stirring, to prevent the surface of the silver nitrite becoming coated with silver iodide. The silver nitrite was ground to a fine suspension, but no reaction occurred.

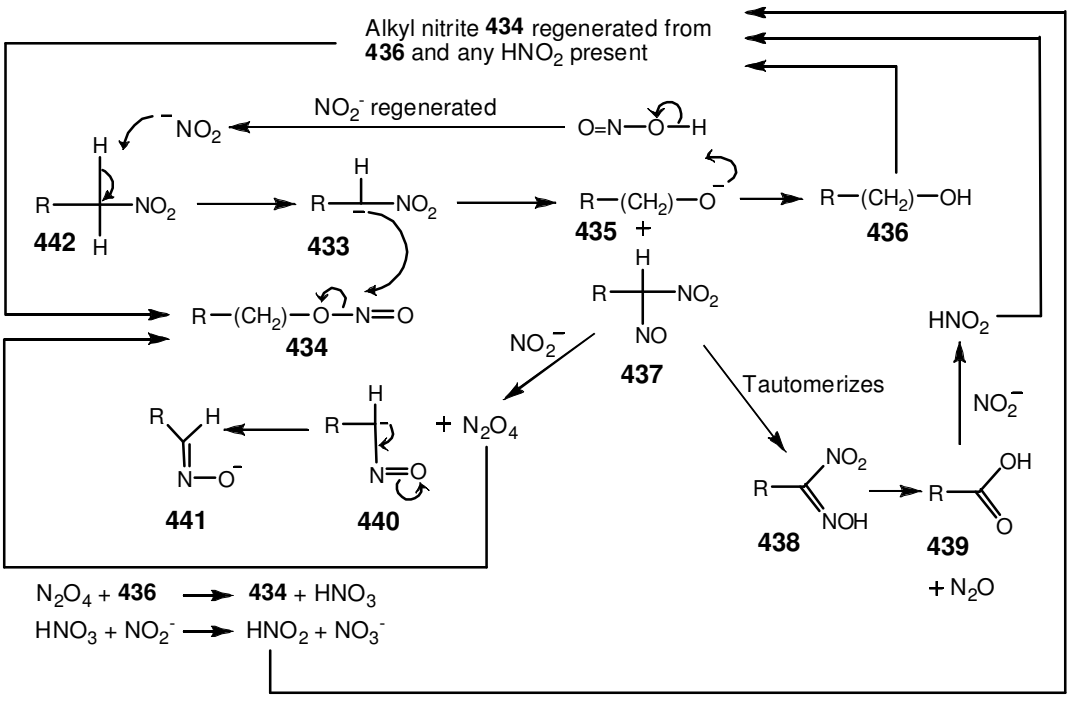
The reaction was next attempted using Kornblum's modification of the Victor Meyer reaction. This uses sodium nitrite instead of silver nitrite, and is performed in DMSO or DMF, in the presence of phloroglucinol (1,3,5-trihydroxybenzene), the latter being used

to suppress side reactions. Kornblum had prepared a sequence of α-nitroesters in this manner.[157]

The reaction was tried (Entry 4) in DMF, and (Entry 5) in DMSO, as was a variation in DMF with urea being used to suppress side reactions.[158] In all three cases only the hydroxyketone **425** was obtained.

Further study of Kornblum's (extensive) earlier investigations into this reaction revealed this result to be unsurprising.[159,160,161] Nitrite esters (if formed) are not merely unwanted by-products but actively catalyse the destruction of the nitro compound.

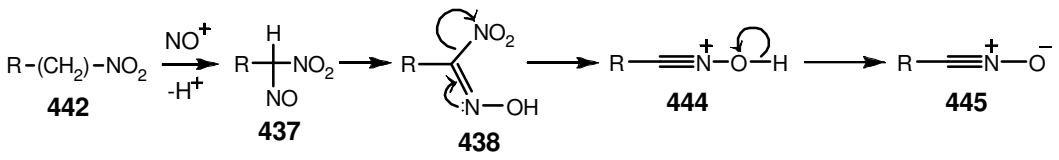
The mechanism[159] is shown in Scheme 83. Nitrite ion acts as a base to deprotonate **442**, the anion of which **433** then attacks the nitrite ester **434** leaving the alcohol **436** and the pseudo nitrole **437**. This may break up in various ways. In the case of R being an alkane,[159] tautomerization to the unstable nitrolic acid **438** occurs. This breaks down to give the carboxylic acid **439** and N_2O.



Scheme 83

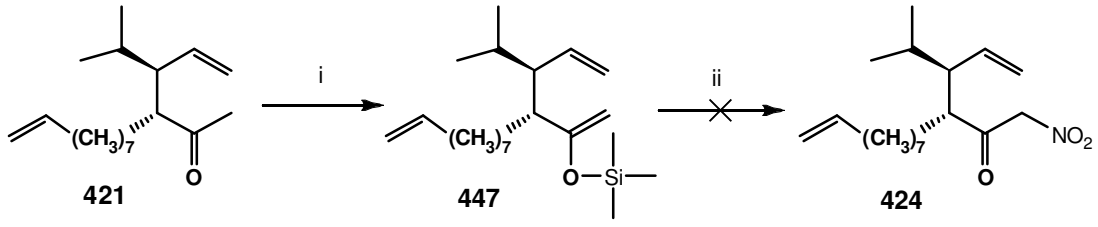
If R is an ester (*i.e.* if **442** is an α-nitroester), the oximinato-ester **440** may be formed,[161] releasing N_2O_4. If there is any HNO_2 available, it is liable to regenerate the nitrite ester **434**. With excess nitrite available, *any* acid (*e.g.* **439**) is going to generate HNO_2. Similarly N_2O_4 will give the nitrite ester, plus nitric acid, which will generate further HNO_2. The nitrite ester is therefore a true catalyst, and can be regenerated by a number of means. The function of the phloroglucinol is to scavenge nitrite ester, by removing the NO. Kornblum and co-workers do not specify exact nature of the product formed, describing it as 'presumably nitroso-phloroglucinol', 'deeply coloured' and 'water soluble'.[160] In the light of these results, this method of preparing **424** was not considered viable.

A nitrile oxide cyclization was reported by Maiti and Bhattacharya, starting directly from an alkyl halide, with acetic acid and sodium nitrite.[162] The proposed mechanism appeared unusual, the nitrile oxide **445** being formed from the nitrolic acid **438** by elimination of H^+ and NO_2 (Scheme 84).



Scheme 84

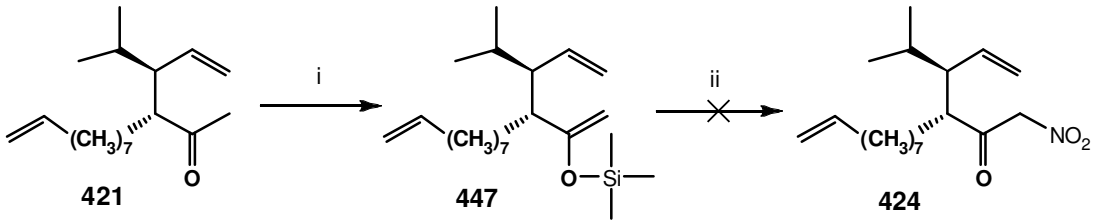
Whilst the reaction described in the reference was *inter*molecular, it seemed worth testing on an *intra*molecular basis. Accordingly it was tried on **423** with the intention of preparing **446** (Scheme 85). Only the hydroxyketone **425** could be isolated.



i) Et_3N, KI, TMSCl,CH_3CN 66% ii) NO_2BF_4, CH_3CN

Scheme 85

Preparation of **424** *via* the silyl enol-ether **447** was next considered (Scheme 83). The preparation of **447** by the method of Campbell and co-workers[163] was successful, with a reasonable yield of 66%.



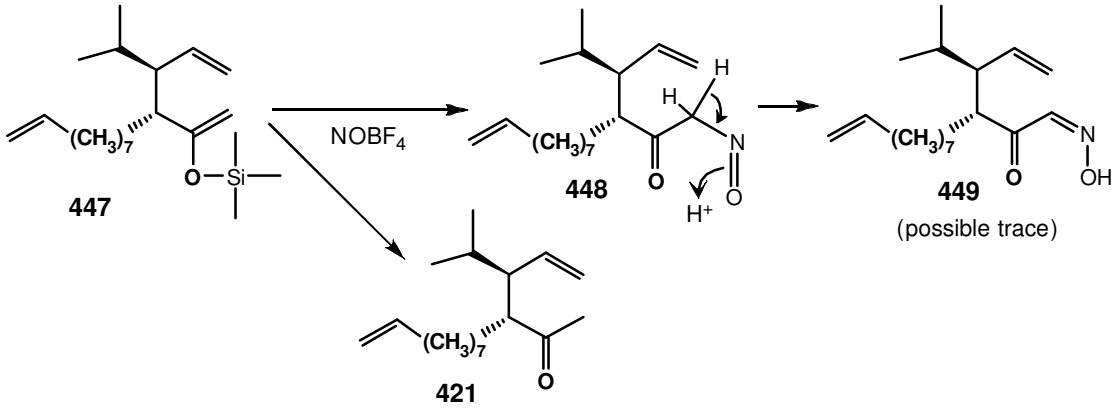
i) Et_3N, KI, TMSCl,CH_3CN 66% ii) NO_2BF_4, CH_3CN

Scheme 86

Nitration of silyl enol ethers has been most widely performed with tetra-nitromethane,[164] however, given the explosive nature of this compound, its use was considered inappropriate.[165] Nitronium tetrafluoroborate has also been used,[166] however, applied to **447** this lead (with 1.2 equivalents) simply to desilylation to **421**, and (in excess) to a multicomponent mixture. This approach was therefore abandoned.

2.4.2 The α-Nitrosoketone and INOC Approach

Referring back to Scheme 75, it was decided to attempt preparation of the nitrile oxide **412** from the oxime **414**. It was considered that the oxime might reasonably (by analogy with Scheme 86) be prepared by nitrosation of **447**, with *nitroso*nium tetrafluoroborate ($NOBF_4$), as in Scheme 87. Whilst there was no direct precedent for the reaction with $NOBF_4$, the same transformation has been performed upon silyl enol ethers using excess NOCl as the nitrosating agent.[167]



Scheme 87

In this case, the major product was desilylation to **421**, however a minor product, with a longer retention time (11.47 minutes) than the silyl enol ether **447** (10.44 minutes) , as would be expected for a more polar compound, was detected by GC-MS (Figure 9).

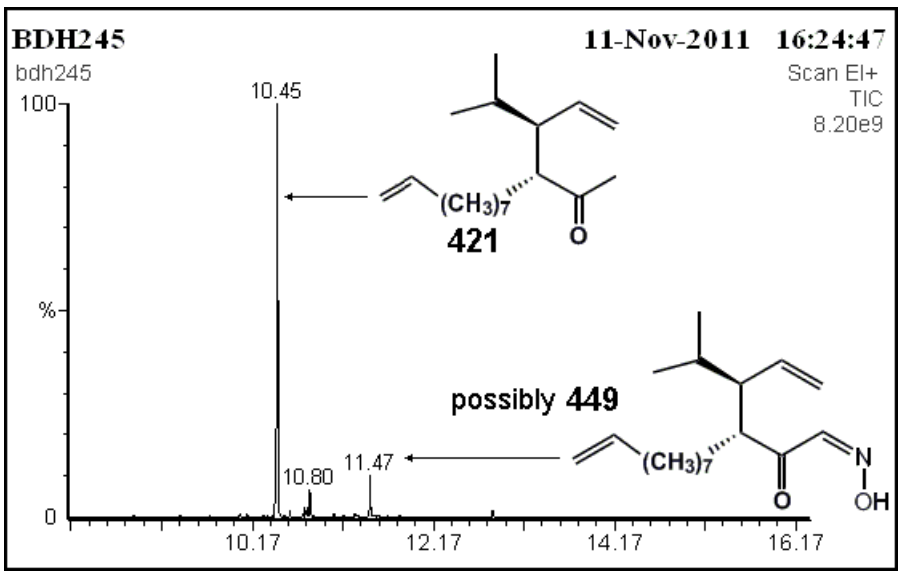


Figure 16

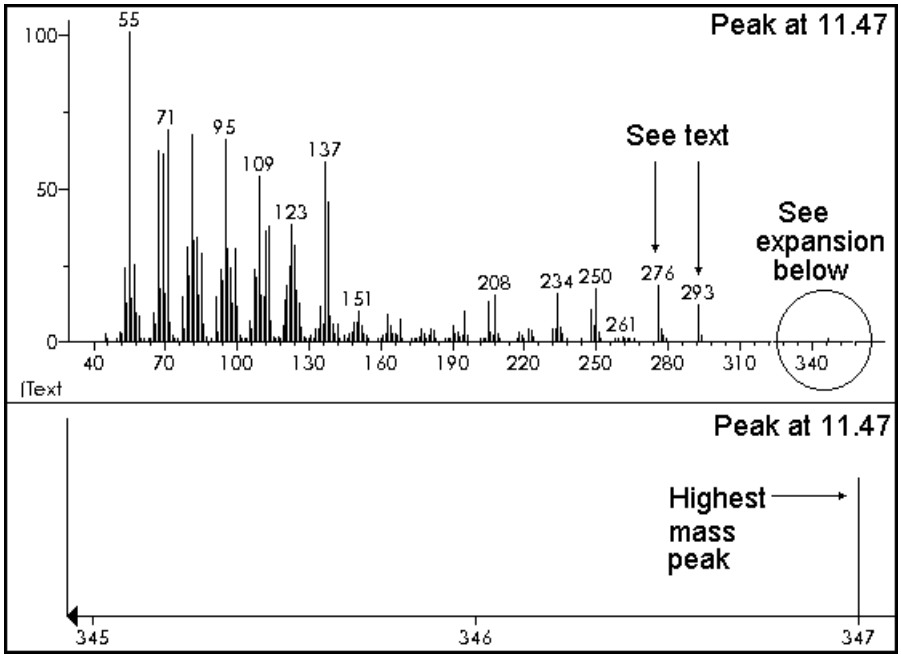
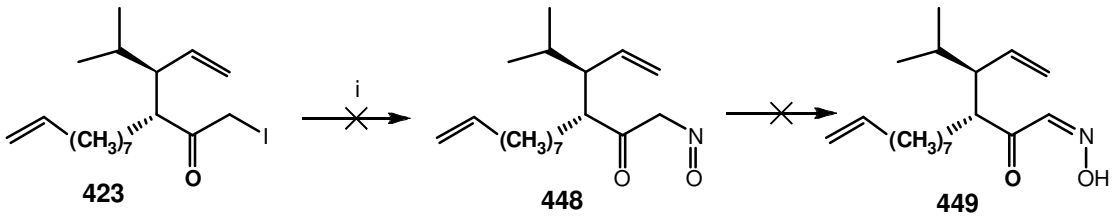


Figure 17

The MS (Figure 17) showed peaks at *m/e* 293 (possibly M^+ of **449**) and at 276 (possibly $[M\text{-}OH]^+$ of **449**), in addition to an unidentified peak at 347.

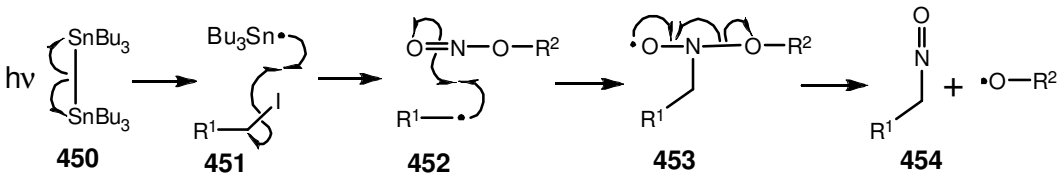
Whilst these results are *consistent* with **449**, and the peak at 347 *may* simply be another minor by-product, they do not constitute positive identification. However, as the proportion (versus that of the desilylated material) detected was very small, and the material appeared to decompose upon work-up, this method of introducing the nitroso or oximino group was considered impractical for preparative purposes and not further investigated.

Finally nitrosation by means of a radical reaction was investigated (Scheme 88).



Scheme 88

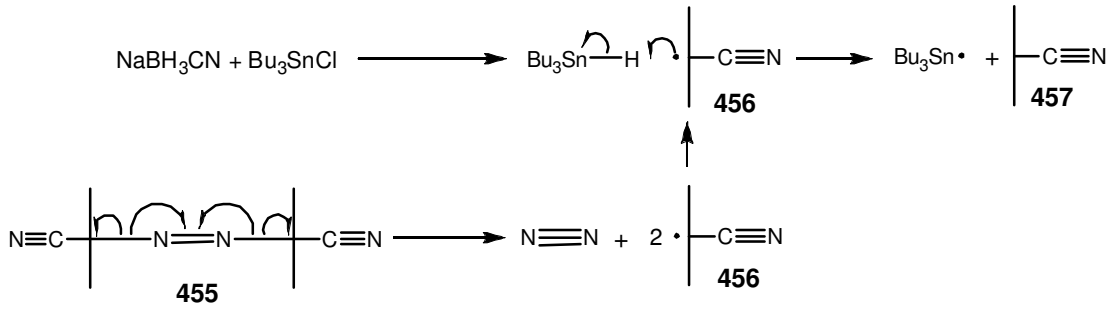
The method, reported by Murphy and Kizil,[168] used hexabutylditin, activated by light, as a source of tributylstannyl radicals. The reference describes the use of *iso*-amyl and *tert*-butyl nitrites, as well as tributylstannyl nitrite, using radicals derived from a number of bromides and iodides, to trap NO (Scheme 89).



Scheme 89

The method was tried with both *iso*-amyl- and *tert*-butyl nitrites. No oxime could be identified in the products. Small quantities of material lacking the vinyl adjacent to the isopropyl (by NMR) were isolated, but the mass spectra were very inconsistent. This material was not further investigated.

The reaction was next attempted under Stork's conditions[169] for generation of tributyltin radicals (Scheme 90). Here, tributyltin chloride and sodium cyanoborohydride are used to slowly generate tributyltin hydride. Azoisobutyronitrile (AIBN) **455** breaks down upon heating to yield two 2-cyanopropyl radicals **456** and nitrogen.



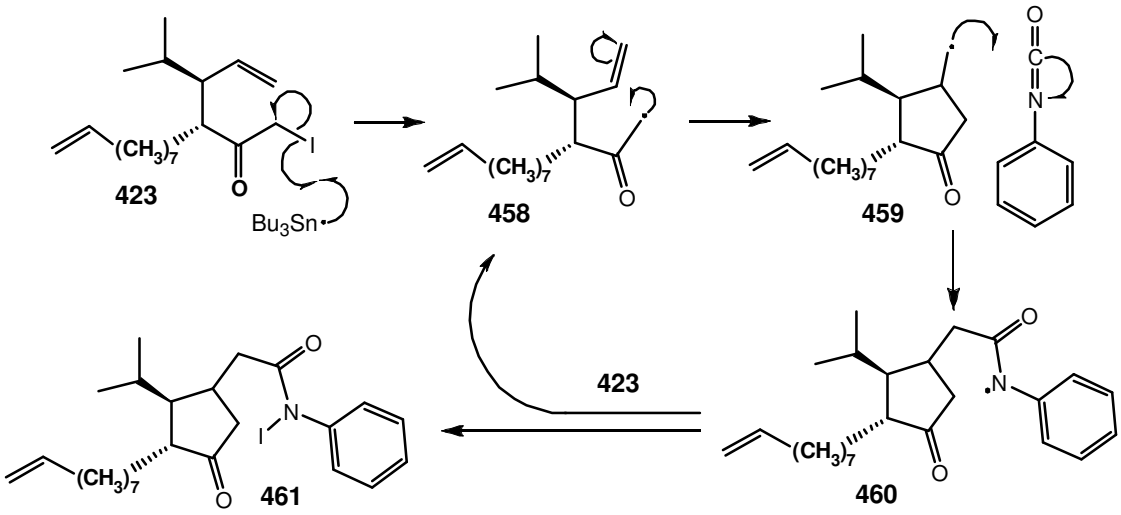
Scheme 90

The 2-cyanopropyl radicals subsequently attack the tributyltin hydride to give tributyltin radicals and isobutyronitrile. The method overall is designed to generate tin radicals slowly and steadily under thermal (rather than photochemical) control. In the paper cited, the radicals generated from the substrate by the tributyltin radicals were used to

trap CN from *tert*-butyl isocyanide. The method was not successful when applied to **423** to trap NO, a mixture of products with no provable trace of the oxime was obtained.

2.4.3 Radical-based approach, trapping by Isocyanate

Trapping of the radical derived from **423** was also attempted with isocyanate (Scheme 91). In principle, the radical **460** resulting from attack on the isocyanate could abstract iodine from another molecule to give **461** (which should be amenable to cyclization by base) and another radical **458**, thereby propagating the chain reaction.

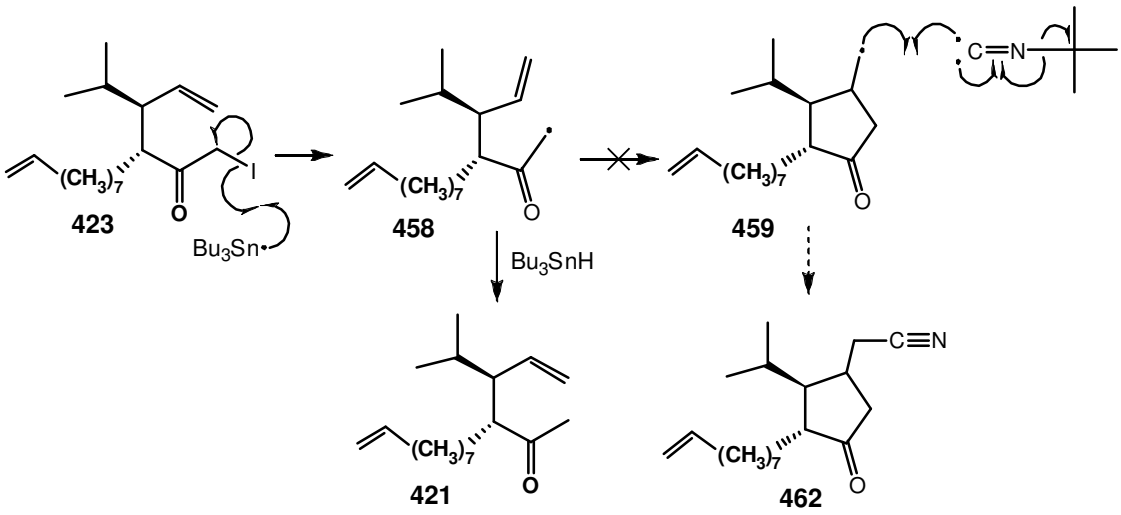


Scheme 91

Phenyl isocyanate was selected as a model because it was available. The reaction was tried (using hexabutylditin and incandescent light), but, whilst, the hexabutylditin and **423** were consumed and three products were visible by GC, none of the associated mass spectra of these products showed any sign of incorporation of the isocyanate. This approach was therefore discontinued.

2.4.4 Radical-based approach, trapping by Isocyanide

Trapping of cyanide was next considered, again using Stork's method, using *tert*-butyl isocyanide as the cyanide source (Scheme 92). This reaction was tried twice, the second time without AIBN. In both cases, whilst **423**, AIBN, Bu_3SnCl, Bu_3SnH, Bu_3SnI, (all identified by MS) could all be clearly seen by GC-MS (Figure 18) the only product derived from **423** that could be isolated (confirmed by low resolution MS on the GC, and high resolution MS of a preparative TLC sample) was the de-iodinated ketone **421**.



Scheme 92

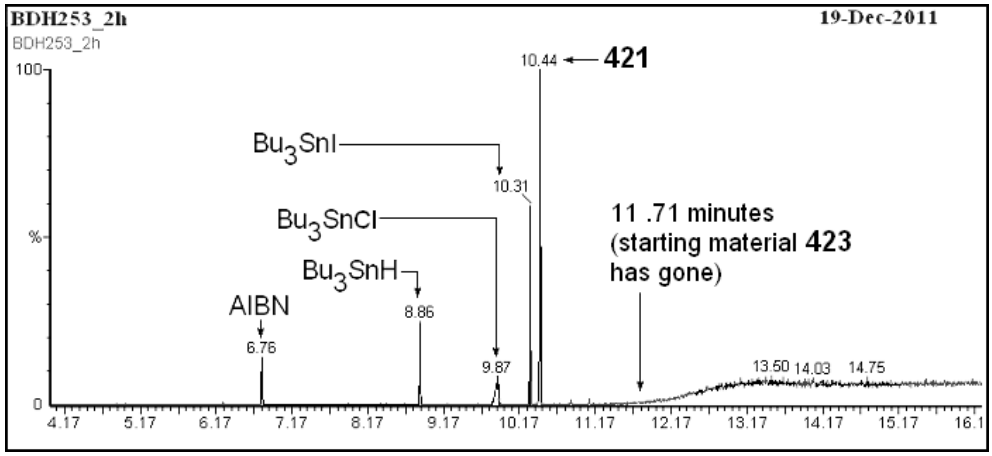


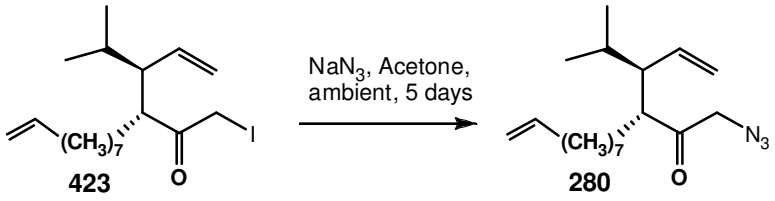
Figure 18

No incorporation of CN could be detected in the IR spectrum. This should be contrasted with the results with nitrites. It is presumed that in the present case, in the *absence* of alkyl nitrite, Bu_3SnH could accumulate, and reached a sufficiently high concentration to effect reduction of the radical **458** to the ketone **421**. Conversely, in the *presence* of alkyl nitrite, any Bu_3SnH not transformed (*via* the tributylstannyl radical) into Bu_3SnI (as desired) would have been 'mopped up' (again, *via* the tributylstannyl radical) by conversion into tributylstannyl nitrite or other oxidation products. That the same result was obtained in the absence of AIBN is somewhat surprising, however, as Bu_3SnH reductions of alkyl halides without the use of an additional initiator such as AIBN have been reported,[176] the use of such an initiator is evidently not always necessary.

The reaction was repeated using hexabutylditin and incandescent light as the source of tributyltin radicals. The results were practically identical to those with phenyl isocyanate; a mixture of three unidentifiable products derived from **423** with no incorporation (by IR) of CN.

2.4.5 Approaches *via* the Azide **280**

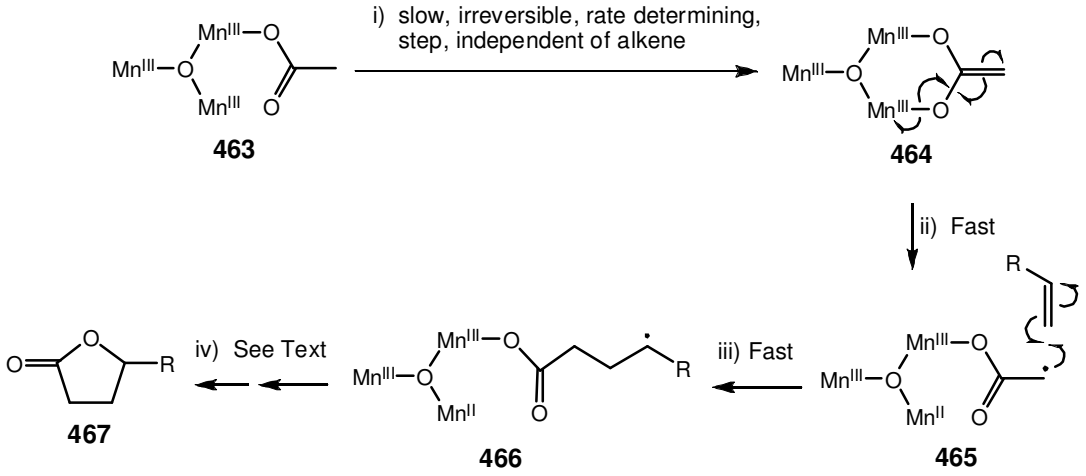
Finally, with time and starting material running out, it was decided to attempt cyclization *via* the azide **280**. This gave two options, that of oxidative cyclization using manganese (III) acetate and that of another try at the azomethine-ylid route (1.3.2). The azide was therefore prepared from **423** (Scheme 93).



Scheme 93

2.4.5.1 Oxidative Cyclization with Manganese (III) Acetate

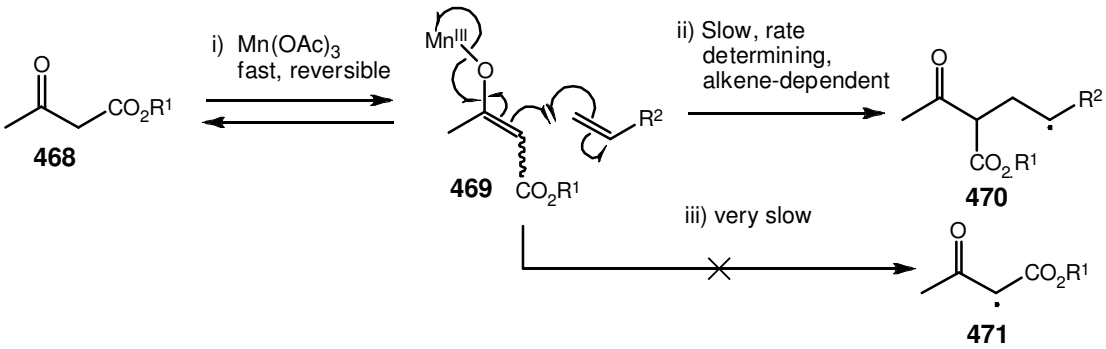
Oxidative addition of acetate to olefins was discovered by Heiba and Dessau,[167] and the method has been widely used.[172,173] The kinetic studies of Snider (and others) upon the mechanism are of interest (Scheme 94).[173] There appear to be two mechanisms. Scheme 94 illustrates the first, in the case of manganese (III) acetate adding acetate to an olefin. Manganese (III) acetate consists of linear chains of oxo-centred trimers with acetate bridges.[174,175] Enolization (step *i*) to **464** is slow, irreversible, and rate-determining, formation (step *ii*) of the radical **465** is fast, as is addition (step *iv*) of the olefin to give the secondary radical **466**.



Scheme 94

The mechanism of the final step (step *iv*) is unknown. It is undoubtedly oxidative, but as Mn(III) is not able to oxidize secondary radicals to cations, the exact details are obscure.[173]

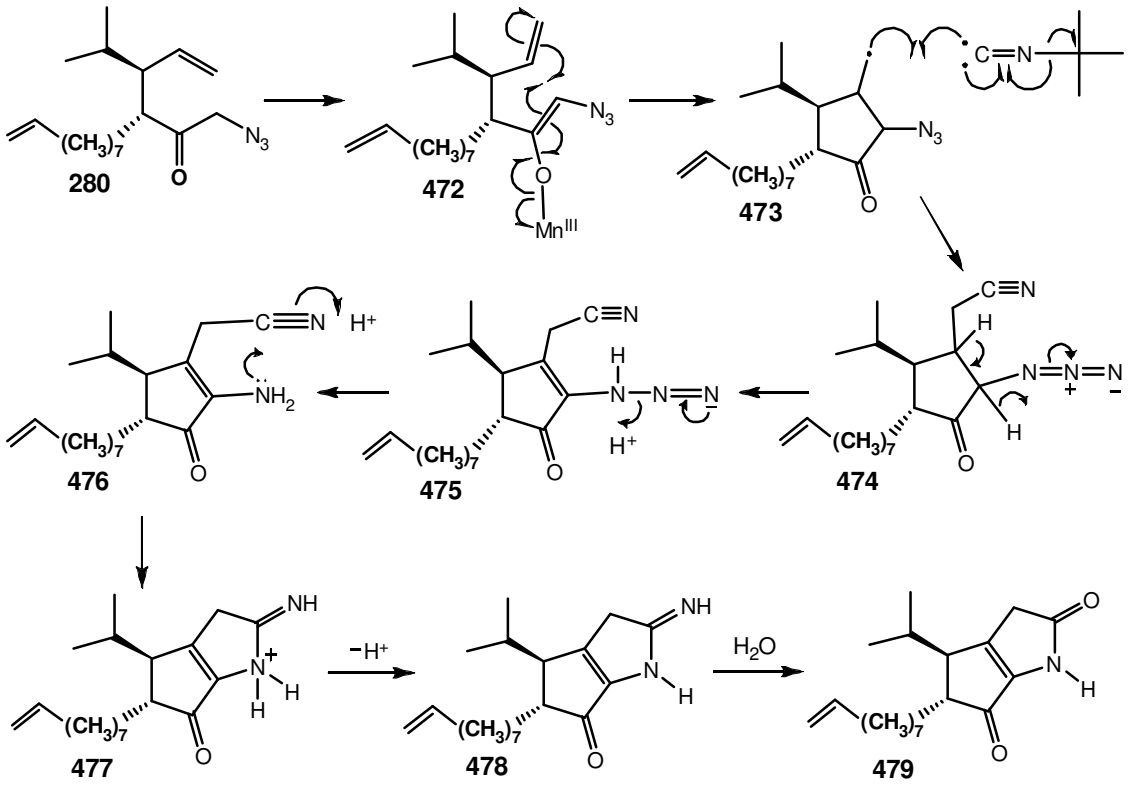
In the case of a more acidic compound (β-ketoester, β-diketone etc *e.g.* **468**) the kinetics are somewhat different (Scheme 95).[173]



Scheme 95

Formation (step *i*) of the enolate **469** is fast and reversible. Attack upon the olefin (step *ii*) is slow, rate-determining and dependent upon the alkene, (*i.e.* the alkene's substitution and, in the case of cyclization, the length of the tether), and presumably proceeds *via* a transition state similar to that shown. Oxidation (step *iv*) of the enolate **469** to the radical species **471** does not seem to be involved. Such oxidations are very slow *e.g.* $Mn(AcAc)_3$ is a stable compound.

With regard to the current project, a route from the azide **280** to the route proposed shown in Scheme 96. Whilst these reactions are commonly performed in acetic acid, it was considered that this would probably destroy the *tert*-butyl isocyanide. Examples[172] were found of these reactions being performed in benzene, therefore this solvent was used.



Scheme 96

The reaction was attempted on an 8mg scale. No cyclized product could be detected, and starting material **280** was recovered. Referring back to Snider's mechanisms, this is consistent with that of Scheme 95. If the enolate **472** had been formed, but the olefin had been unable to approach sufficiently close to react, recovery of starting material would be expected, given the enolate formation is known to be reversible, and the enolate would be expected to be stable in the absence of a suitably positioned olefin.

GC during the reaction indicated (apparent) formation of di-*tert*-butyl urea, presumably from oxidation of the *tert*-butyl isocyanide by the manganese(III)acetate. A 'blank' reaction (with no **280**) was run simply to test the stability of *tert*-butyl isocyanide under these conditions. This confirmed that some di-*tert*-butyl urea was formed (GC-MS and IR matched authentic material prepared form *tert*-butyl isocyanate and *tert*-butylamine) as well as polymeric material. The reaction (with **280**) was tried again using ethanol as a solvent. Again, no trace of cyclized material could be detected. This approach was therefore discontinued.

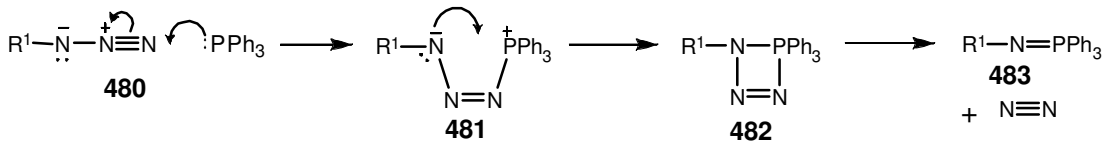
2.4.5.2 The Aza-Wittig and Azomethine Ylid Approach

This approach has briefly been discussed in 1.3.2, the results being the subject of the previous publication[53] by Viseux, Parsons and co-workers. Given the availability of the azide, it was decided to retry this approach.

The route may conveniently be divided into three parts, the Staudinger reaction, the aza-Wittig reaction, and the azomethine-ylid.

2.4.5.2.1 The Staudinger Reaction

This was discovered by Staudinger in 1919.[51] The mechanism[176] involves the attack of a phosphane (usually triphenylphosphine) upon an azide, as shown in Scheme 97.

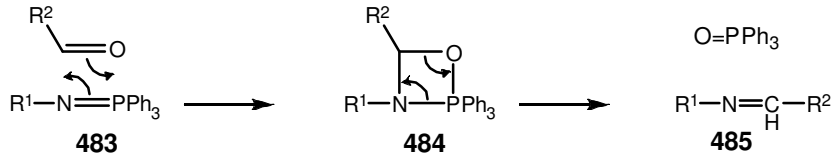


Scheme 97

The reaction, its exact mechanism, and the structure and conformation of the phosphazide **481** have been the subject of investigation, reviews[177,178] and computational studies.[179,180] Phosphazides **481** have been isolated, but they readily extrude nitrogen to give the compounds **483**, known as iminophosphoranes, phosphazenes or 'Staudinger Intermediates'. These compounds are readily hydrolysed to amines and triphenylphosphine oxide, and the reaction is sometimes used to effect R-Hal to R-NH_2 as an alternative to the Gabriel (and analogous) reactions (See 1.3.4.2). Their present interest, however, is their ability to participate in the aza-Wittig reaction.

2.4.5.2.2 The Aza-Wittig Reaction

The aza-Wittig reaction (Scheme 95), was also discovered by Staudinger,[51] who obtained phenyl isocyanate from the reaction of phenyl aza-ylid (R^1=Ph, R^2=O) with carbon dioxide, although the term 'aza-Wittig reaction' is obviously more recent; the actual Wittig reaction (2.1.1.1) not having been discovered until 1954.[58]



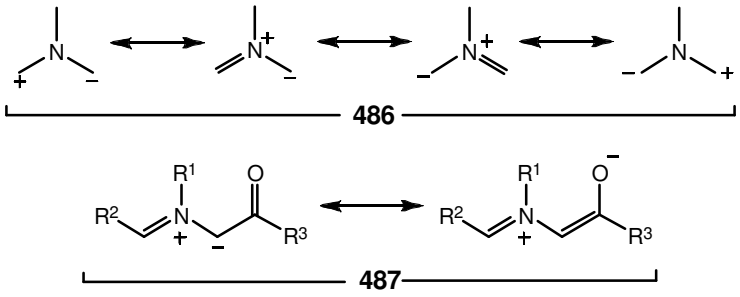
Scheme 98

The reaction has been widely applied[52] in recent years, as a method of installing a C=N bond under mild conditions, just as the analogous HWE and Wittig reactions are for installation of C=C. The exact details of its mechanism are not well known, as the intermediates are unstable, although there have also computational studies.[52]

2.4.5.2.3 Azomethine Ylids

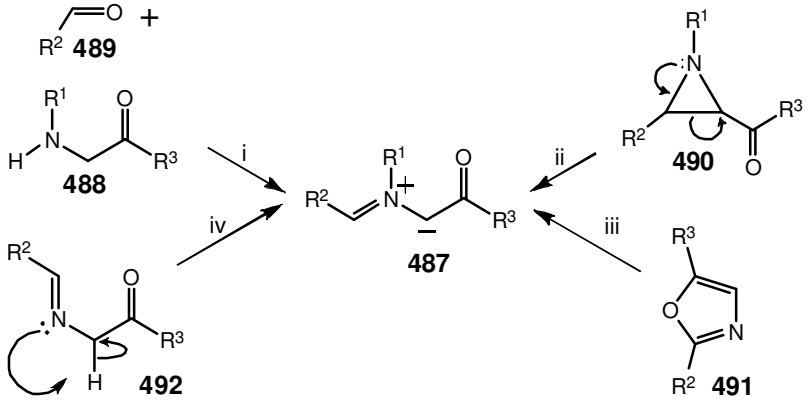
Azomethine ylids are reactive 1,3-dipoles. 1,3-Dipolar cycloadditions were first recognized as a specific *class* of reaction by Huisgen,[181] although many examples of the class (*e.g.* ozonolysis) were actually known. Sustman[182] classified 1,3 dipolar cycloadditions into three categories on the basis of the frontier molecular orbital interactions. In Type 1 reactions, the HOMO of the dipole reacts with the LUMO of the dipolarophile. This is analogous to the situation with 'ordinary' Diels-Alder reactions. Type 3 is where the LUMO of the dipole reacts with the HOMO of the dipolarophile, analogous to the 'inverse electron demand' Diels Alder (as used by Boger, see 1.2.11). Type 2 covers reactions which may go *via* either route. Azomethine ylid cycloadditions are Type 1 in the Sustman classification.

In an azomethine ylid **486** the nitrogen atom has a carbon either side, one bearing a formal positive charge, the other a formal negative one (Scheme 99). The position of the formal charges may be exchanged by resonance. The ylid may be further stabilized by an EWG *e.g.* carbonyl, as in **487**.



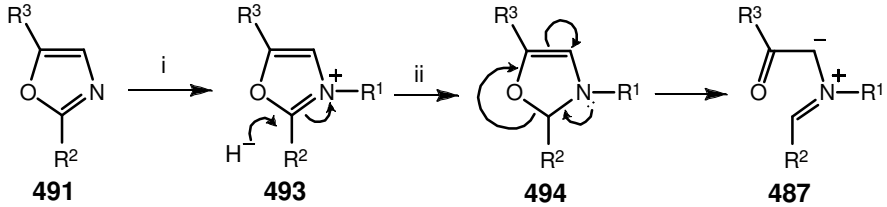
Scheme 99

Stabilized azomethine ylids may be prepared by a number of routes,[183] four of the most important (and relevant) ones being shown in Scheme 100.



Scheme 100

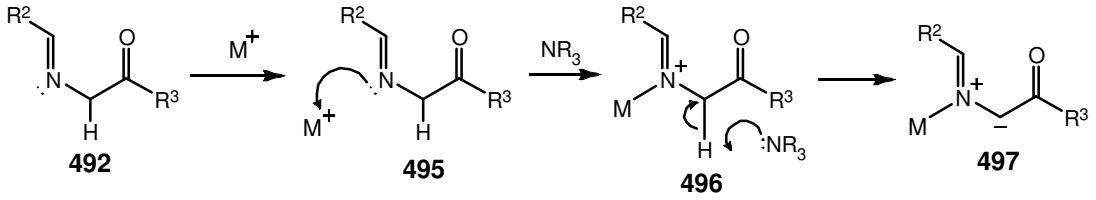
They may be prepared from aldehydes **489** by condensation with a suitable secondary amino acid derivative **488**, from a suitably substituted aziridine **490**, and from certain heterocycles, *e.g.* an oxazole **491** (see 1.3.3), by quaternization and reduction (Scheme 101).



i) Quaternization (eg R^1I); ii) Hydride reduction

Scheme 101

Finally, they can be prepared (Scheme 97 (*iv*)) from imines (preparable in turn *via* the aza-Wittig reaction) in various ways. Scheme 100 shows the formation by a prototropic shift. They may also be made by alkylation and deprotonation (essentially equivalent to the preparation *via* the aldehyde, which may be regarded as 'arrested imine formation) or by metalation, as in Scheme 102.

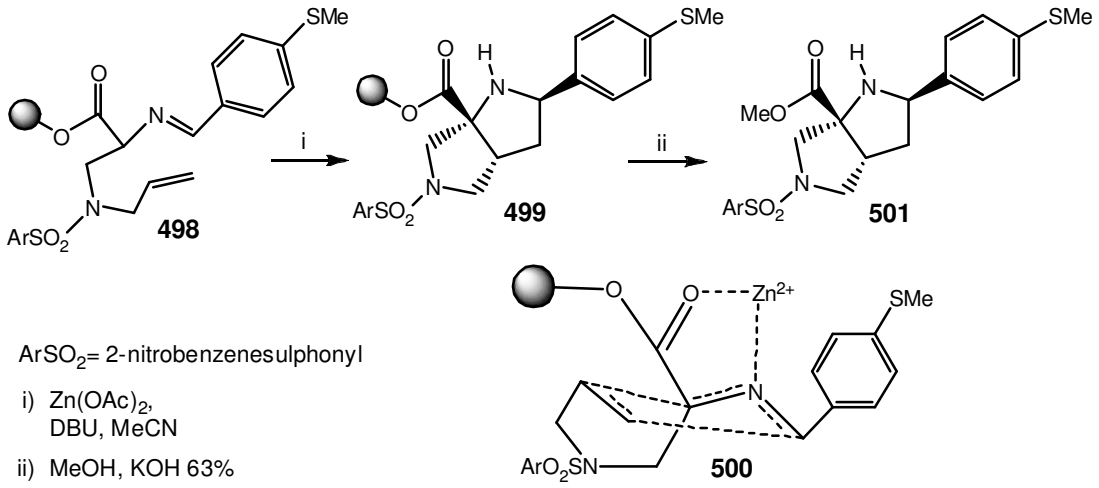


Scheme 102

Various metal salts may be used (LiCl, AgOAc), and the metalated imine **496** may then be deprotonated with a suitable base (*e.g.* an amine) to give **497**, the azomethine ylid.

As stated earlier, cycloadditions of these azomethine ylids are Type 1, like a 'normal' Diels Alder reaction, and given the stabilized negative charge, they prefer to react with electron deficient double bond. To paraphrase, the reaction works best when the dipolarophile double bond is 'activated' by an EWG. This is entirely consistent with the findings of Viseux[53] described in 1.3.2. The azomethine ylid would only react with an activated double bond. In Scheme 28, this was an external trap, ethyl acrylate, in the presence of silver acetate, which gave **228**. In Scheme 29, the internal double bond of **229** was activated by CO_2Et, which gave **230** in the presence of magnesium sulfate.

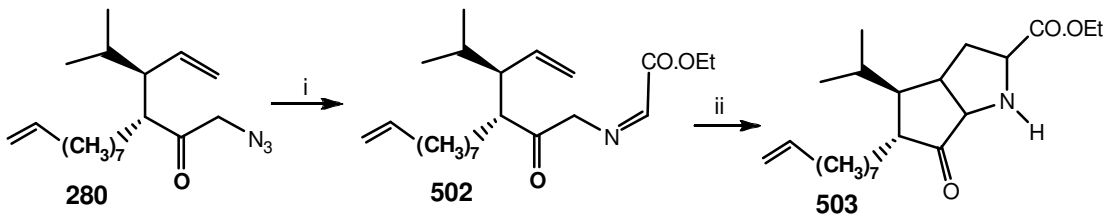
On this basis, an attempt to cyclize **423** without activation of the double bond appeared very unlikely to work. However, a publication by Gallop was found[184] (Scheme 103) in which zinc (as zinc acetate) was used to metalate an imine **495**, DBU was used to deprotonate the metalated imine, and the resultant azomethine-ylid underwent cycloaddition (*via* the transition state **500**) with the tethered olefin to give the bicycle **499**.



Scheme 103

The reaction had further interesting features, in addition to the use of zinc. It was performed on a resin (in this case, hydroxymethyl polystyrene resin, which had been esterified with the precursor to **498** using 1,3-diisopropylcarbodiimide and DMAP) from which **499** was released to give **501** using methanol/KOH. Most importantly, it will be seen that the olefin dipolarophile was not activated. The authors draw attention to this specific point in their paper:- *"While intermolecular additions to stabilized ylids of this type require electron withdrawing groups for activation of the dipolarophile, the intramolecular versions appear comparatively insensitive to the electronic character of the olefin component."*

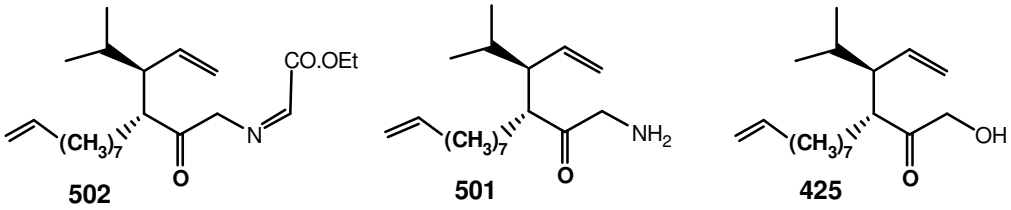
This had *not* been found to be the case (1.3.2, Scheme 28 and Scheme 29) with the roseophilin system. On this basis, it could be that the highly-hindered roseophilin system was a less amenable substrate, or that the zinc-promoted azomethine ylid cyclization system was better than others hitherto tried. In the hope that the latter was the case, it was decided to try this reaction with the last of the azide (Scheme 104).



Scheme 104

Unfortunately, the only definitely identifiable product (by MS and NMR) was triphenylphosphine oxide. NMR showed much $O{=}PPh_3$, together with a mixture of products evidently derived from **280**, including at least four carbonyls, one aldehydic. IR, after subtracting the triphenylphosphine oxide peaks showed carbonyl bands, but no azide.

None of the products considered likely to result from failed cyclization could be identified by MS (Figure 19).



502 **501** **425**

Figure 19

Reasons for the failure are unknown. Glyoxylates are unstable, and known to polymerise (although the polymerisation would appear to be reversible) however the sample used had been distilled from P_2O_5 two hours prior to use and kept at -78°C in the interim.[185]

This reaction used up the last of the available azide, therefore this approach had to be discontinued.

2.5 Conclusions

Whilst the practicality of developing a total synthesis of roseophilin based upon the Ireland Claisen rearrangement has not been proven, much methodology that would be required for such a synthesis has been established. The required alcohol **284** can now be prepared economically in bulk. The use of an anion exchange resin in expediting the work-up of Ireland-Claisen reactions has proven successful. The Ireland Claisen reaction most extensively studied (**360** → **363**) did not prove particularly satisfactory, however the feasibility of performing this reaction upon a robust, accessible substrate **360** to give an equally robust rearrangement product, stable to extensive purification, has been established. Similarly, the conversion of the terminal double bond of **363** to a more usefully-functionalized material **408** by has been demonstrated.

Installation of nitrogen by the nitroketone (2.4.1) or nitrosoketone (2.4.2) routes does not appear practical, neither do the radical approaches (2.4.3 and 2.4.4) based upon the iodoketone **368.** The oxidative cyclization (2.4.5.1) with manganese (III) acetate does not appear promising, however the aza-Wittig approach via the azide **280** has so far received only preliminary investigation, and may yet prove a fruitful approach.

Chapter 3 Experimental

General Experimental Procedures

Unless otherwise stated, all reactions were conducted under nitrogen, using oven-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. DMPU was distilled from calcium hydride, and stored in the dark over freshly-activated 4Å molecular sieve, under nitrogen.

TLC was conducted on Merck Kieselgel 60 0.25 mm glass-backed TLC plates. Visualization was by iodine vapour, or phosphomolybdic acid dip (in ethanol) unless otherwise stated. Column chromatography (MPLC) was performed on Fisher 60Å, 35-70 micron silica

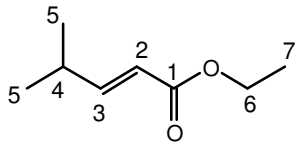
NMR spectra were taken on a Varian VNMRS 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) or Varian VNMRS 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C). Chemical shifts for ^{1}H are reported in parts per million relative to residual $CDCl_3$ (δ = 7.26 ppm). Chemical shifts for ^{13}C are reported relative to $CDCl_3$ (central line of triplet at δ = 77.00). The following abbreviations are used to describe the multiplicity of given signals; s = singlet, d = doublet, t = triplet, quint = quintet, sex = sextet, oct = octet, m = multiplet, br = broad. Strongly coupled proton signals were analysed and the coupling constants and corrected chemical shifts calculated by the methods described by Hoye and co-workers[186,187] and Reich,[188] or, in other cases, solved by simulation.[99] Numbering of atoms in structures is arbitrary. Multiplicities (C,CH,CH_2,CH_3)were determined by HSQC.

IR spectra were taken on a Perkin Elmer Spectrum One FTIR

Gas Chromatographs (GC) were taken on a Perkin Elmer Autosystem XL, using an HP5M5 Column (30m, 1/4mm ID, ¼ micron film).

High resolution mass spectra (Acc. Mass.) were taken on a Bruker Daltonics Apex 3 (4.3T, +ve ESI). Low resolution mass spectra were taken on a Fisons Instruments Autospec (+ve EI 70 ev) or (in the case of GC-MS) a Perkin Elmer Turbomass (EI).

E-Ethyl-4-methylpent-2-enoate **287**



Appearance: colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ

6.94 (1H, dd, J = 15.8, 6.4 Hz, 1-H), 5.77 (1H, d, J = 15.8 Hz, 2-H), 4.18 (2H, q, J = 7.0 Hz, 6-H), 2.39-2.53 (1H, m, 4-H), 1.29 (3H, t, J = 7.0, 7-H), 1.07 (6H, d, J = 6.7 Hz, 5-H)

^{13}C (125 MHz, $CDCl_3$) δ

167.03 (1-C), 155.37 (3-CH), 118.62 (2-CH), 60.11 (6-CH_2), 30.89 (4-CH_2), 21.21 (5-CH_3), 14.25 (7-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2964, 1717 (C=O), 1651(C=C), 1466, 1367, 1299, 1263, 1189, 1164, 1133, 1036, 984, 861

Acc Mass (ESI): $C_8H_{15}O_2$ MH^+

Calc: 143.1067

Found: 143.1066 Error: - 0.39 ppm

R_f 0.4 (9:1 40/60 petroleum ether:diethyl ether)

GC-MS

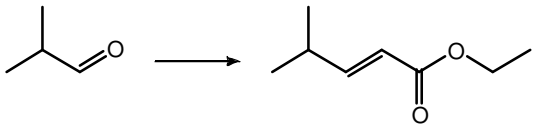
HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 6.2 minutes (*vs* retention time for Z-isomer 5.5 minutes under the same conditions)

Mass Spectrum (EI, Low resolution, integral with GC)

142 (M^+), 114 (M^+ -C_2H_4) 97 (M^+ -EtO), 69 (M^+ -CO.OEt) 41 ($C_3H_5^+$)

Spectroscopic data consistent with literature[48,49]



Procedure 1: (Aqueous Sodium Carbonate Method)[48,49]

Anhydrous sodium carbonate (63.5 g 0.6 mol) was warmed with deionised water, (total volume 100 ml) to dissolve, cooled to room temperature with stirring, and the resultant slurry diluted with a further 20 ml deionised water. This was cooled to approximately 10°C (cold water bath) then triethyl phosphonoacetate (38 ml, 42.9 g, 0.187 mol,) and 22 ml isobutyraldehyde (17.46 g 0.242 mol) added *en masse.* The slurry was stirred for four days under nitrogen, then extracted with diethyl ether (200 ml in four portions), the combined organic extracts washed with brine (40 ml) and dried over sodium sulfate, and the solvents removed at 40°C under reduced pressure. The resultant oil was purified by chromatography on silica gel (hexane, then 7% diethyl ether in hexane). Yield (of >97% *E*-isomer material by GC) 11.7 g, 44.1%. A further 6% was isolated as mixed isomers (2.54g of 62% *E* 38% *Z* by GC)

Procedure 2: (Lithium *t*-Butoxide Method)[77]

(Bulk reaction, one of a number done on a similar scale. The products of these reactions were not individually purified, but were combined for kugelrohr distillation)

Hexane* (400 ml) was placed in a 1 litre 3-neck flask, equipped with two septa and a thermometer, and flushed with nitrogen. *tert*-Butanol (14.8 g 0.2 mol) was added, the whole cooled to –30°C (slush bath, acetone/water/liquid N_2) and n-butyl lithium in hexane (80 ml 0.2 mol) added over 5 minutes (exotherm to –10°C), the reaction cooled to –20°C, then stirred at 0°C for 30 minutes. The reaction was then cooled to -20°C, and triethyl phosphonoacetate (44.8 g 0.2 mol) added over 2 minutes, causing an exotherm to –10°C. When the exotherm had subsided the reaction was allowed to warm to 0°C and the suspension (thick white precipitate) stirred at 0°C for 1h.

The reaction was then cooled to –30°C and isobutyraldehyde (12.5 ml, 9.93 g, 0.138 mol) added *en masse*, and the reaction allowed to reach 0°C and stirred for 2 hrs, after which period the suspension had largely cleared. The reaction was cooled to –30°C and 100ml 50% saturated sodium hydrogen carbonate solution (equal volumes saturated sodium hydrogen carbonate solution and water) added, causing an exotherm

to 0℃. The phases were separated, the aqueous phases extracted with diethyl ether (2 x 100ml), and the combined organic phases washed successively with 50% saturated sodium hydrogen carbonate solution (1 x 150 ml), then brine (2 X 150 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. A clear oil remained.

GC showed desired product to be present in 39:1 *E:Z* ratio, plus other minor impurities, and the triethyl phosphonoacetate. The yield was not determined at this stage, the product was combined with those of other reactions for distillation.

Kugelrohr Distillation.

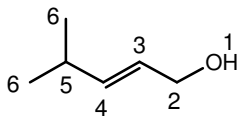
The products of a number of reactions as described in Procedure 2 (0.138 mol x 3 and 0.165 mol = 0.573 mol of isobutyraldehyde) were combined and subjected to kugelrohr distillation, with an oven temperature of 20°C at a pressure of 20 torr. Yield 50.57 g (61.9%) of title compound (*E:Z* ratio of 32:1 by GC) was obtained.

Procedure 3: Methyl Magnesium Bromide Method (Recommended procedure)[78]

Triethyl phosphonoacetate (6.72 g, 0.03 mol) was dissolved in dry THF and cooled to -35° , and methyl magnesium bromide solution (3M solution in diethyl ether, 10 ml, 0.03 mol) added by syringe over 2 minutes. The reaction was allowed to warm to ambient temperature over 40 minutes, then cooled to -35°C, and isobutyraldehyde (3 ml, 2.37 g, 0.0329 mol) added *en masse*. The reaction was allowed to warm to ambient, then heated (under a *slow* stream of nitrogen to remove ether vapour) to 55-60°C for 5 hr. The reaction was cooled to 0°C, and diethyl ether (50 ml) added followed by saturated ammonium chloride solution (10 ml). The phases were separated, and the organic phase washed successively with portions of saturated sodium metabisulfite (10 ml x 4), saturated sodium hydrogen carbonate (10 ml x 6), brine (10 ml x 4), dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure, adding and evaporating several changes of dichloromethane to the residue in order to purge the residual THF. Product pale brown oil, no trace of *Z*-isomer by GC, 3.59 g 84%.

The products of a number of similar reactions (1.004 mol total) were combined and distilled (20 torr, 81°C, vacuum-jacketed fractionating column) to give 129.4 g of title compound, 90%.

E-4-Methyl-pent-2,3-enol **284**



Appearance: colourless oil

Boiling point 60°C, 19 torr[189]

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.67 and 5.59 (2H, $ABXY_2$ system J = 15.5, 6.5, 5.8 Hz, 4-H and 3-H respectively), 4.06 (2H, d J = 5.7 Hz, 2-H), 2.31 (1H, app. oct. J = 6.7 Hz, 5H), 1.40 (1H, bs, 1-H), 1.00 (6H, d, J = 6.8 Hz, 6-H)

^{13}C NMR (125 MHz, $CDCl_3$) δ

140.29 (4-CH), 125.90 (3-CH), 63.87 (2-CH_2), 30.65 (5-CH), 22.18 (6-CH_3)

IR (thin film, ν_{max} cm^{-1}) 3308 broad (OH), 1466, 1364, 1078, 1010, 969 (C=C)

Acc mass not obtainable (compound is too volatile)

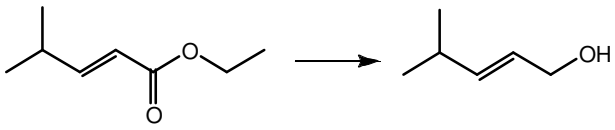
GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 4.47 min

Mass spectrum (EI Low resolution, integral with GC)
82 $(M\text{-}H_2O)^+$, 69 $(M - CH_2\text{-}OH)^+$, 67, 57, 41

Spectroscopic data consistent with literature[48,49]



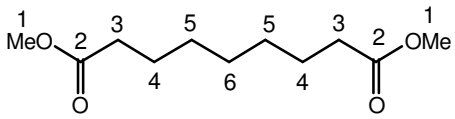
E-Ethyl-4-methylpent-2-enoate **287** (15 g, 0.105m) was dissolved in dry 3:1 dichloromethane:diethyl ether mixture (400 ml), placed in a 2 litre 3-neck flask fitted with a pressure-equalizing dropping funnel, stirrer, magnetic stirrer, thermometer and a slow nitrogen purge) and cooled to -78°C. DIBAL (1M solution in diethyl ether, 250 ml, 0.25 mol) was then added dropwise over 90 minutes, and the reaction maintained at -78°C for a further 3 hr. At the end of this period, the magnetic stirrer bar was removed, and *fast* overhead paddle stirrer inserted, whilst maintaining the cardice/acetone cooling. Cold (0°C) aqueous sulfuric acid (45 g concentrated acid diluted to 350 ml) was added over two minutes with *vigorous* stirring of the slurry, the addition being exothermic and hydrogen being evolved, the reaction allowed to warm to 20°C over approximately 15 minutes and the stirring maintained. After stirring for 1 hr at 20°C a *clear* (no solids and no gas evolution) biphasic system was obtained. This was extracted with diethyl ether (2 X 300 ml) and the combined organic phases washed with approximately 150ml portions of brine (x1), saturated sodium hydrogen carbonate (x1), brine (x4), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. Yield 11.97 g crude, 114% due to residual solvents.

The products of three reactions as above (2 x 0.105 mol = 0.315 mol total) were combined for fractional distillation (jacketed column) at 20 torr. Mixed fractions distilled below 50°C, clean material at 60°C. 22.5 g of clean (no *Z*-isomer by GC) material (76.4%) was obtained, together with a mixed fraction 2.56 g (6.5:1 *E/Z*). This mixed fraction represents 6.7% (of the total, 0.315 mol) *E* isomer, and 1.2% of the *Z*-isomer.

Note that literature[189] boiling points (56-56.8°C (*Z*-isomer) and 57-57.5°C (*E*-isomer) both at 20 torr) differ by only 1°C, hence some co-distillation is practically inevitable.

Dimethyl nonane-1,9-dioate **329**

(Dimethyl Azelate)[82]



Appearance: colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ
3.66 (6H, s, 1-H), 2.29 (4H, t, J = 7.5 Hz, 3-H), 1.57-1.65 (4H, m, 4-H), 1.27-1.35 (6H, m, 5 & 6-H)

^{13}C (125 MHz, $CDCl_3$) δ
174.1 (2-C), 51.34 (1-CH_3), 33.97 (3-CH_2), 28.85 (5 or 6-CH_2), 28.80 (5 or 6-CH_2), 24.79 (4-CH_2)

IR (thin film, ν_{max} cm^{-1}) 2935, 2859, 1734 vs C=O, 1436, 1361, 1195, 1168, 1098, 1057, 1033, 883, 728

Acc Mass (ESI): $C_{11}H_{21}O_4$, MH^+

Calc: 217.1434

Found: 217.1436 Error: - 0.58 ppm

GC-MS

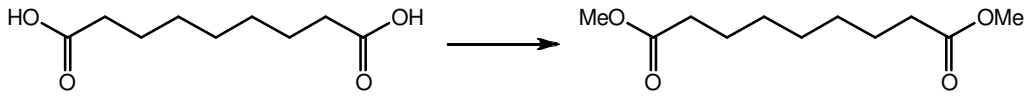
HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 9.16 min

Mass Spectrum (EI, Low resolution, integral with GC)

185,152,143,124,111

Commercially available compound. Spectroscopic data consistent with literature.[192]



Procedure 1:
(Method of Rao and co-workers[82] for this compound with very minor modifications.)

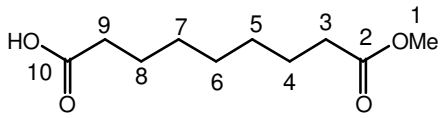
Azelaic acid (48.6 g 0.258 mol) was dissolved in methanol (150 ml), concentrated sulfuric acid (4 ml) added, the reaction vessel purged with nitrogen, boiled under reflux for 24 hr, then left overnight room temperature. The clear, colourless solution was concentrated to approximately 50-60 ml under reduced pressure, then poured into approx 200 ml ice/water, then solid sodium hydrogen carbonate added (CO_2 evolved) to pH7 and the remaining ice was allowed to melt. The mixture was extracted with dichloromethane (4 x 200 ml), the organic phases combined, and washed with successive 100 ml portions of 50% saturated sodium hydrogen carbonate solution (x1) and brine (x2), dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. 47.1 g, 84.4%

Procedure 2:
Recovery of mixed acid/esters as Dimethyl Azelate **329**

Aqueous liquors and concentrated methanolic fractions from various preparations of methyl hydrogen azelate (containing a maximum of 0.0932 mol of azelate, calculated by difference from isolated yields) were combined, and acidified with concentrated hydrochloric acid to pH1-0. The mixture was extracted sequentially with dichloromethane (100 ml) and ethyl acetate (7 x 100 ml), the organic phases combined, and washed with brine (2 x 100 ml), dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was dissolved in methanol (100ml), heated to boiling, and left to cool to ambient temperature for 1h. The solvent was then removed under reduced pressure, further methanol (100 ml) added, boiled, and then left for 1h, the solvent removed and the process repeated. After three exchanges of solvent, further methanol (80 ml) and concentrated sulfuric acid (1 ml) were added, and the reaction heated under reflux under nitrogen overnight. The solvent was then removed under reduced pressure, dichloromethane (100 ml) and water (100 ml) added, the phases separated and the aqueous phase extracted with further dichloromethane (3 x 100ml). The combined organic phases were washed with

brine (1 x 50 ml), saturated sodium hydrogen carbonate (1 x 50 ml), brine (2 x 50 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. 20.1 g 99%.

Monomethyl Nonane-1,9-dioate
(Methyl Hydrogen Azelate) **330**[82]



Appearance: colourless semisolid

^{1}H NMR (500 MHz, $CDCl_3$) δ

3.66 (3H, s, 1-H), 2.34 (2H, t, J = 7.5 Hz, 9-H), 2.30 (2H, t, J = 7.5 Hz, 3-H), 1.55-1.7 (4H, m, 4 & 8-H), 1.28-1.39 (6H, m, 5,6 & 7-H)

^{13}C (125 MHz, $CDCl_3$) δ

179.73 (10-C), 174.27 (2-C), 51.43 (1-CH_3), 34.01 (3 or 9-CH_2), 33.94 (3 or 9-CH_2), 28.86 (5,6 or 7-CH_2), 28.80 (5,6 or 7-CH_2), 29.79 (5,6 or 7-CH_2), 24.81 (4 or 8-CH_2), 24.54 (4 or 8-CH_2).

Carbons 2 & 10, and 3 & 9 differentiated by HMBC

IR (thin film, ν_{max} cm^{-1}) 2933, 2856, 1736 (Ester C=O*), 1690 (Acid C=O),1468, 1435, 1410, 1252, 1195, 917

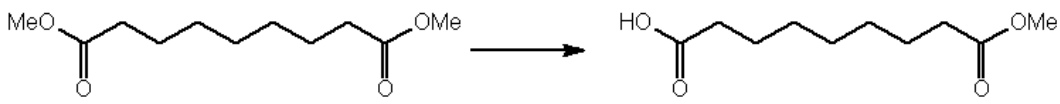
*compare 1734 in diester **329**. Remaining carbonyl is therefore the acid.

Acc Mass (ESI): $C_{10}H_{18}O_4Na$

Calc: 225.1097

Found: 225.1093 Error: 1.77 ppm

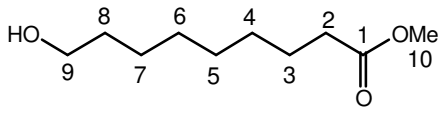
Commercially available compound . Spectroscopic data consistent with literature.[193]



Method of Rao and co-workers[82] with minor modifications.

Barium hydroxide octahydrate, freshly recrystallized from water to remove carbonate, (56.0 g 0.178 mol) was dissolved in methanol (1 litre) in a conical flask. A solution of dimethyl azelate (80.0 g, 0.317 mol) in methanol (200 ml) was then added. The reaction was placed under nitrogen, and stirred at room temperature. The initially-clear solution began to cloud after about 30 minutes, and the stirring was continued for 24 hr. The precipitate was collected by filtration, sucked and pressed (under a rubber dam) as dry as possible, washed with methanol and then with hexane, then sucked dry for 30 minutes. The solid was then suspended in 500 ml deionized water, and acidified (using 6N hydrochloric acid, dropwise) with vigorous stirring to pH3, correcting excursions of pH with a few drops of barium hydroxide solution as and when necessary. When pH had stabilized at pH3 the aqueous phase was extracted with dichloromethane (200 ml X3), the combined organic phases washed with brine (100 ml X2), separated, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure to give a semi-crystalline oil. 60.42 g, 72%

Methyl 9-Hydroxy Nonanoate **331**



Appearance: yellowish oil

^{1}H NMR (500 MHz, $CDCl_3$) δ

3.33 (3H, s, 10-H), 3.63 (2H, t, J = 6.1 Hz, 9-H), 2.29 (2H, t, J = 6.1 Hz, 2-H), 1.59-1.65 (2H, m, 3-H), 1.53-1.58 (2H, m, 8-H), 1.27-1.38, (10H, m, 4,5,6 & 7H)

^{13}C (125 MHz, $CDCl_3$) δ

174.26 (1-C), 62.96 (9-CH_2), 51.39 (10-CH_3), 34.05 (2-CH_2), 32.71 (8-CH_2), 29.15 (4,5,6 or 7-CH_2), 29.14 (4,5,6 or 7-CH_2), 29.01 (4,5,6 or 7-CH_2), 25.62 ((4,5,6 or 7-CH_2), 24.87 (3-CH_2)

IR (thin film, ν_{max} cm^{-1}) 3419 br (OH), 2929, 2855,1737 vs (C=O), 1436, 1337, 1197, 1172, 1055, 725

Acc Mass (ESI):

Calc: $C_{10}H_{20}O_3$ Na 211.1305

Found: 211.1302 Error: 1.45 ppm

R_f 0.2 (2:1 Hexane:Dichloromethane))

GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 8.98 minutes.

Mass Spectrum (EI, Low resolution, integral with GC)

158,138, 87, 74, 69, 55

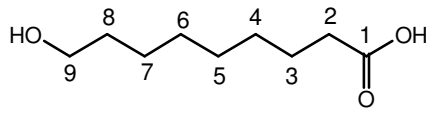
Trace of nonane-1,9-diol at 8.77 min (Identified by 'fingerprinting' from onboard library of spectra on GC)

Spectroscopic data consistent with literature.[48]

Method of Viseux,[48] with minor modifications.

A solution of methyl hydrogen azelate in (24.8 g 0.123 mol) in dry THF (250 ml) was cooled to -78°C, and borane/THF complex (140 ml of 1M solution in THF, 0.140 mol) was added over 1 hr (syringe pump) maintaining the temperature between -78°C and -60°C. The reaction was kept at -78°C for an hour, then allowed to reach ambient temperature and left for 48 hr. The reaction was then poured into saturated aqueous sodium hydrogen carbonate solution, extracted with dichloromethane (3 x 100 ml), washed with 3 x 100 ml brine, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. 20.85 g, 90%.

9-Hydroxynonanoic acid **336**



Appearance: white solid

Melting point 46.5-49°C Lit[190] 53-54°C

^{1}H NMR (500 MHz, $CDCl_3$) δ

4.50-6.50 (2H, bs, O-H and CO.OH), 3.63 (2H, t, J = 6.7 9-H), 1.59-1.67 (2H, m, 3-H), 1.52-1.59 (2H, m, 8-H), 1.26-1.39 (8H, m, 4,5,6, & 7-H)

^{13}C (125 MHz, $CDCl_3$) δ

179.17 (1-C), 62.89 (9-CH_2), 33.98 (2-CH_2), 32.54 (8-CH_2), 29.09 (x2 not resolvable, 4,5,6 or 7-CH_2), 29.90 (4,5,6 or 7-CH_2), 25.57 (4,5,6 or 7-CH_2), 24.63 (4,5,6 or 7-CH_2)

IR (solid, ν_{max} cm^{-1}) 3405 OH br, 3332 OH br, 2931 vs, 2851 vs, 1688 C=O, 1433 1409, 1334, 1297, 1228, 1057 vs, 979, 919, 637

Acc Mass (ESI):

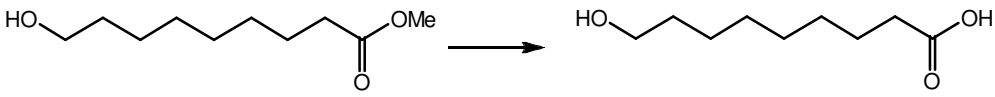
Calc:$C_9H_{18}NaO_3$ 197.1148

Found: 197.1147 Error: 0.73 ppm

Mass Spectrum (EI, Low resolution)

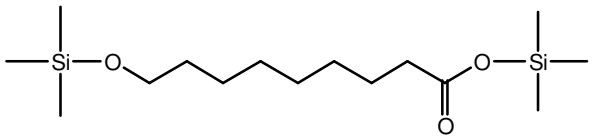
157 ($(M-OH)^+$), 144, 138, 97, 69, 55

Spectroscopic data consistent with literature.[191]



Potassium hydroxide (0.2 g, 0.0036 mol) was dissolved in water (1 ml), methyl 9-hydroxynonanoate **331** (0.42 g 0.00223 mol) dissolved in methanol (2 ml) added, and stirred overnight under nitrogen at ambient temperature. The methanol was then evaporated under reduced pressure, diethyl ether and water (20 ml of each) added, stirred, and the phases separated. The aqueous phase was washed with a further 20 ml of diethyl ether, then acidified to pH1-0 and extracted with dichloromethane (3 x 10 ml). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. 0.16 g, 41%

Trimethylsilyl 9-trimethylsilyoxynonanoate **337**



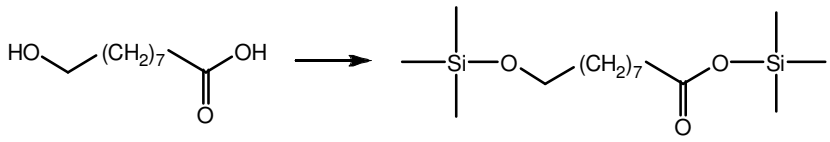
This compound was not fully characterized. It was prepared solely in dilute solution as a reference sample for GC work.

GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 9.79 minutes

Mass Spectrum (EI, Low resolution, integral with GC).
No molecular ion (318) could be detected. 303 ($M\text{-}CH_3^+$), 287 ($M\text{-}(CH_3$ and $O)^+$), 213, 147, 73 ($(CH_3)_3Si^+$)

Literature[194] gives no spectral data for this compound.

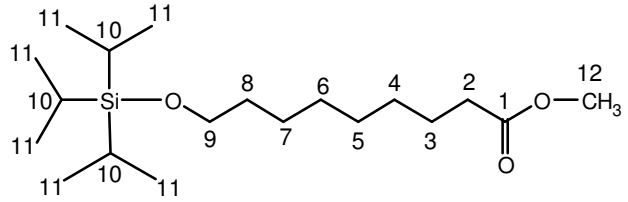


Approximately 3 mg of 9-hydroxynonanoic acid **336** was dissolved in approx 0.5 ml of dichloromethane in a 2 ml GC sample vial, which was then sealed with a septum.

A 'silylating solution' was prepared by diluting a 1 ml ampoule[86] of 99% bis-trimethylsilyl trifluoromethyl acetamide (BSTFA) and 1% TMSCl with 80 ml dry dichloromethane. This solution was thereafter kept sealed and under nitrogen.

Approximately 0.5 ml of 'silylating solution' was added *via* syringe and left at ambient temperature for 24 hrs. The solution was used directly as a GC reference sample, the chromatogram showing the title compound and excess BSTFA.

Methyl 9-(triisopropylsilyloxy)nonanoate **332**



Appearance: colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

3.65-3.70 (5H, m, 12 & 9-H), 2.31 (2H, t, J = 7.1 Hz, 2-H), 1.59-1.67 (2H, m, 3-H), 1.50-1.58 (2H, m, 8-H), 1.26-1.39 (8H, m, 4,5,6 & 7-H), 1.0-1.15 (21H, m, 10 & 11-H)

^{13}C (125 MHz, $CDCl_3$) δ

174.27 (1-C), 63.45 (9-CH_2), 51.38 (12-CH_3), 34.10 (2-CH_2), 32.98 (8-CH_2), 29.24 (4,5,6 or 7-CH_2), 29.22 (4,5,6 or 7-CH_2), 29.08 (4,5,6 or 7-CH_2), 25.74 (4,5,6 or 7-CH_2), 24.94 (3-CH_2), 18.01 (11-CH_3), 12.03 (10-CH)

IR (thin film, ν_{max} cm^{-1}) 2932 vs, 2865 vs, 1743 vs (C=O), 1463, 1247, 1201, 1104 vs, 882 vs, 680 v

Acc Mass (ESI):

Calc: $C_{19}H_{14}O_3Si$ 345.2819

Found: 345.2813 Error: 1.91 ppm

R_f 0.5 (1:1 40/60 petroleum ether:dichloromethane)

<u>GC-MS</u>

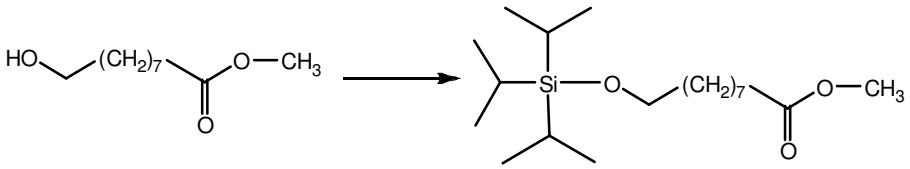
HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.63 min

Mass Spectrum (EI, Low resolution, integral with GC)

No molecular ion 313 (M-OCH_3^+), 301 (M-$C_3H_7^+$), 269, 157 (M-$C_3H_7)_3Si^+$), 145

Spectroscopic data consistent with literature.[48]

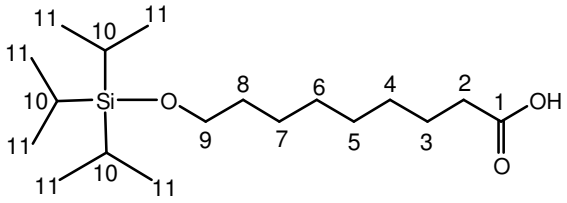


Procedure 1: Method of Viseux[48]

Methyl 9-hydroxynonanoate **331** (7.52 g, 0.04 mol) and 2,6-lutidine (distilled, 17.12 g 0.16 mol) dissolved in dry dichloromethane (50 ml), placed under nitrogen and cooled to -50°. Triisopropyl triflate (17.13 g, 0.056 mol) was then added, followed by a further 10ml dichloromethane. The reaction was allowed to warm to 0-4°C (ice bath) and maintained at this temperature for 3 hrs. The reaction was then poured into 15% citric acid solution (50 ml), water (50 ml) and diethyl ether (100 ml) added, vigorously stirred and the pH carefully adjusted with a few drops of 2N hydrochloric acid to pH1-2. The organic phase was separated, the aqueous phase extracted with further diethyl ether, the combined organic phases washed with brine (100 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. A brown oil remained. GC showed title compound, a small quantity of an unidentified impurity, TIPS-OH, but no trace of starting material. The yield not determined at this point. The product was used directly for preparation of 9-triisopropylsilyloxynonanoic acid **333**.

A small sample was purified for characterization

9-Triisopropylsilyloxynonanoic acid **333**



Appearance: brownish oil

^{1}H NMR (500 MHz, $CDCl_3$) δ

3.68 (2H, t, J = 6.6 Hz, 9-H), 2.35 (2H, t, J = 7.5 Hz, 3-H), 1.6-1.7 (2H, m, 3-H), 1.5-1.6 (2H, m, 8-H), 1.3-1.4 (8H, m, 4,5,6 & 7-H), 1.0-1.16 (21H, m, 10 & 11-H)

^{13}C (125 MHz, $CDCl_3$) δ

179.47 (1-C), 63.44 (9-CH_2), 33.93 (2-CH_2), 32.97 (8-CH_2), 29.22 (4,5,6 or 7-CH_2), 29.2 (4,5,6 or 7-CH_2), 28.99 (4,5,6 or 7-CH_2), 25.74 (4,5,6 or 7-CH_2), 24.65 (3-CH_2), 18.01 (11-CH_3), 12.03 (10-CH)

IR (thin film, ν_{max} cm^{-1}) 2931 vs, 2864 vs, 1709 C=O vs, 1463, 1101, 882, 680

Acc Mass (ESI):

Calc: $C_{18}H_{38}O_3Si$ 353.2482

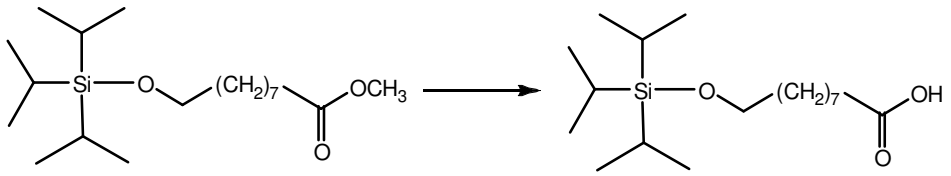
Found: 353.2475 Error: 2.14 ppm

R_f 0.15 (neat dichloromethane)

Mass Spectrum (EI, Low resolution)

331 (MH^+), 313, 287, 269, 243

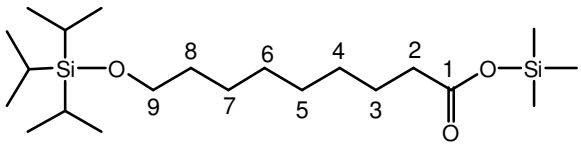
Spectroscopic data consistent with literature.[48]



Method of Viseux,[48] modified.

Crude methyl 9-(triisopropylsilyloxy)nonanoate **332**, (prepared as previously described, theoretically containing 0.177 mol, plus TIPS-OH) was dissolved in methanol (400 ml), cooled to 0° and a solution of potassium hydroxide (15.0 g, 0.267 mol in 54 ml water) added, and the reaction stirred under nitrogen overnight. The solvent was then removed under reduced pressure. Water (220 ml) was then added, then citric acid (17.0 g, 0.089 mol) added with vigorous stirring. The pH was adjusted by careful dropwise addition of 6N hydrochloric acid, maintaining vigorous stirring, to bring the pH to 1.5-2. The biphasic system was then separated, the aqueous phase extracted with further diethyl ether (2 x 200 ml) and the combined organic phases washed with 50/50 brine/water (2 x 10 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by chromatography (initially in dichloromethane/hexane, then in ethyl acetate/hexane. 23.7 g, equating to 40.5% over 2 steps, **331** → **332** → **333**.

Trimethylsilyl 9-(triisopropylsilyloxy)nonanoate **334**
(novel)



This compound was not fully characterized. It was prepared solely in dilute solution as a reference sample for GC work.

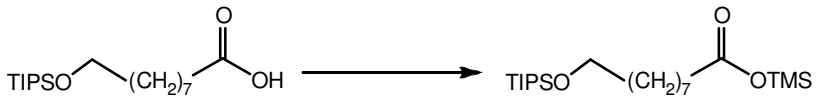
GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.63 minutes

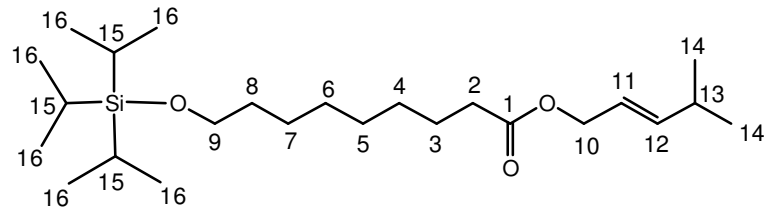
Mass Spectrum (EI, Low resolution, integral with GC).

No molecular ion (402) could be detected. 387 $[M\text{-}CH_3]^+$, 359 $[M\text{-}C_3H_7]^+$, 269, 203
73 $[(CH_3)Si]^+$



Approximately 3 mg of 9-triisopropylsilyloxynonanoic acid **333** was dissolved in approximately 0.5 ml of dichloromethane in a 2 ml GC sample vial, which was then sealed with a septum. Approximately 0.5 ml of silylating solution (see preparation of **337**) was added *via* syringe and left at ambient temperature for 24 hrs. The solution was used directly as a GC sample, showing the title compound and excess BSTFA.

(*E*)-4-Methylpent-2-enyl-9-(triisopropylsilyloxy)nonanoate **326**



Appearance: yellowish resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.73 (1H, dd J= 15.5, 6.5, 12-H), 5.51 (1H, dt, J = 15.7, 6.5, 11-H), 4.51 (2H, d, J = 6.4 10-H), 3.66 (2H, t, J = 6.7), 2.28-2.35 (3H, m, 13 & 2-H), 1.58-1.68 (2H, m, 3-H), 1.49-1.56 (2H, m, 8-H), 1.28-1.35 (8H, m, 4,5,6 & 7-H), 1.05-1.08 (21H, m 10 & 11-H), 1.0 (6H, d, J = 6.6 14-H)

^{13}C (125 MHz, $CDCl_3$) δ

173.62 (1-C), 143.00 (12-CH), 121.05 (11-CH), 65.11 (10-CH_2), 63.44 (9-CH_2), 34.45 (2-CH_2), 32.98 (8-CH_2), 30.72 (13-CH), 29.26 (4,5,6 or 7-CH_2), 29.23 (4,5,6 or 7-CH_2), 29.07 (4,5,6 or 7-CH_2), 25.74 (4,5,6 or 7-CH_2), 24.95 (3-CH_2), 21.99 (14-CH_3), 18.00 (16-CH_3), 12.02 (15-CH)

IR (thin film, ν_{max} cm^{-1}) 2937 vs, 2865 vs, 1737 C=O vs, 1463, 1383, 1163, 1100 vs, 1057 vs, 1032 vs, 1013, 971, 881, 679

Acc Mass (ESI):

Calc: $C_{24}H_{48}O_3NaSi$ 435.3265

Found: 435.3270 Error: -1.25 ppm

R_f 0.3 (3:1 hexane:dichloromethane)

<u>GC-MS</u>

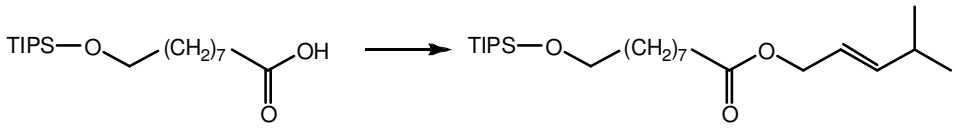
HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 12.50 minutes

Mass Spectrum (EI, Low resolution, integral with GC)

287, 269, 243

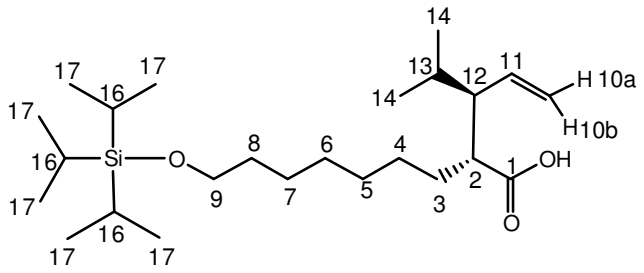
Spectroscopic data consistent with literature[48]



Method of Viseux[48]

9-Triisopropylsilyloxynonanoic acid **333** (23.0 g, 0.0697 mol), E-4-Methyl-pent-2,3-enol **284** (7.67 g, 0.0767 mol), dry dichloromethane (350 ml), 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (16.0 g, 0.0838 mol) and 4-pyrrolidopyridine (7 ml of 10% solution in dichloromethane, catalyst) were combined under nitrogen and stirred for 2 hr at 0°, then the cooling removed, and the clear solution allowed to remain for 24 hr at ambient temperature. The reaction was then diluted with 1 litre of dichloromethane, and washed with 50/50 water/brine, 10% citric acid solution (x 3), then 50/50 water/brine all in approximately 150 ml portions. The solution was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by chromatography using hexane/dichloromethane as eluent. 10.6g 37%

(*R**)-2-((*S**)-4-Methylpent-1-en-3-yl)-9-(triisopropylsilyloxy) nonanoic acid **327**



This material was isolated in trace amount by preparative TLC. The sample was highly contaminated with solvents and DMPU[195] by ^{1}H NMR and insufficient for a ^{13}C NMR to be obtained. A number of peaks in the proton spectrum could, however, be identified.

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.67 (1H, dt, J = 17, 10 Hz, 11-H), 5.08 (1H, d, J = 10 Hz, 10a-H), 4.98 (1H, d, J = 17 Hz, 10b-H), 3.66 (2H, t, J = 6.79, 9-H), 1.03-1.07 (21H, m 16 & 17-H), 0.94 (3H, d, J = 7.4 Hz, 14a/b-H), 0.81 (3H, d, J = 7.4 Hz, 14a/b-H)

These are in agreement with those obtained from this compound by Viseux,[48] and very similar to those obtained from similar compounds by the author.

IR (thin film, ν_{max} cm^{-1}) 2929 vs, 2865 s, 1707 s C=O, 1607, 1462 s, 1104, 882 vs, 679 vs 657 s

The most significant band (carbonyl) at 1707 is in agreement with the literature figure (1705), however, given DMPU, ethyl acetate, and acetone were present in the sample, this result should be treated with caution.

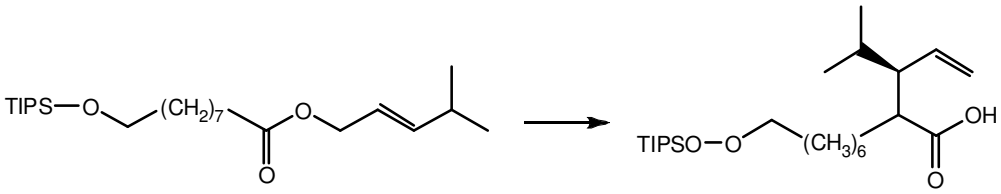
Rf 0.1 (Dichloromethane + 1% formic acid)

Acc Mass (ESI):

Calc: $C_{24}H_{49}O_3Si$ 413.3445

Found: 413.3441 Error: 1.12 ppm

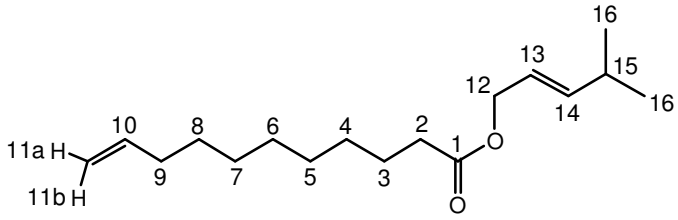
This compound may be regarded as identified, but not fully characterized.



Method of Viseux[48] with modifications.

Lithium hexamethyldisilazide (1M in THF, 4.9 ml, 0.0049 mol) was placed in a 30 ml 2-necked flask (equipped with a septum, nitrogen purge, and a thermometer), cooled to 0°C and *dry* (see General Experimental) DMPU (N,N'-dimethyl-N,N'-propylene urea) (4.8 ml) added. The whole was then cooled to -78°C. (*E*)-4-Methylpent-2-enyl-9-(triisopropylsilyloxy)nonanoate **326** (1.0 g 0.00243 mol) dissolved in *dry* THF (1ml), was then added over 15 minutes, maintaining vigorous stirring, and maintained at this temperature for 1 hr. Chlorotrimethylsilane (distilled from calcium hydride *immediately* prior to use) (0.9 ml, 0.77 g, 0.0071 mol) was then added, followed by trimethylsilyl trifluoromethanesulfonate (0.05 ml, 0.00276 mol), the stirring being maintained and the reaction kept below -60°. The reaction was then kept at -78°C for 1 hr, then 1,2-epoxybutane (0.15 ml, 0.125 g, 0.00173 mol) added, the cooling removed and the reaction allowed to remain at ambient temperature for 24 hr. The reaction was then poured into a mixture of ice (10 g) and 20% citric acid solution (10 ml), stirred and the pH adjusted (with 2N hydrochloric acid, one drop at a time) to pH1-2. The reaction was extracted with diethyl ether (3 x 20 ml), the combined organic phases washed with brine (3 x 20 ml), and then dried over sodium sulfate. The solvent was removed under reduced pressure. TLC indicated a mixture of products and starting material. TLC in an acidified eluent (dichloromethane + 1% formic acid) showed another very minor product just above the baseline. An aliquot was taken and subjected to preparative TLC (dichloromethane + 1% formic acid), and extracted from the silica with ethyl acetate. This minor product was the title compound. Yield not determined.

(*E*)-4-methylpent-2-enyl undec-10-enoate **360**
(novel)



Appearance: Colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.80 (1H, ddt, J = 16.9, 10.2, 6.7 Hz, 10-H), 5.73 (1H, dd, J = 15.5, 6.4 Hz, 14-H), 5.51 (1H dt, J = 15.5, 6.4 Hz, 13-H), 4.98 (1H, d, J = 17.1 Hz, 11b-H), 4.92 (1H, d, J = 10.1 Hz, 11a-H), 4.51 (2H, d, J = 6.5 Hz, 12-H), 2.25-2.36 (3H, m, 15 & 2-H), 2.02 (2H, app q, J = 7.0 Hz), 1.20-1.45 (10H, m, 4,5,6,7 & 8-H), 1.00 (6H, d, J = 6.6 Hz, 16-H)

^{13}C (125 MHz, $CDCl_3$) δ

173.6 (1-C), 143.00 (14-CH), 139.13 (10-CH), 121.04 (13-CH), 114.09 (11-CH_2), 65.10 (12-CH_2), 34.34 (2-CH_2), 33.74 (9-CH_2), 30.72 (15-CH), 29.25 (4,5,6,7 or 8-CH_2), 29.16 (4,5,6,7 or 8-CH_2), 29.08 (4,5,6,7 or 8-CH_2), 29.01 (4,5,6,7 or 8-CH_2), 28.87 (4,5,6,7 or 8-CH_2), 24.94 (3-CH_2),21.99 (16-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2925, 2856, 1736 C=O, 1641, 1463,1164 vs, 1056, 1033s 970 vs, 908 vs

Acc Mass (ESI):

Calc: $C_{17}H_{30}O_2Na$ 289.2138

Found: 289.2135 Error: 0.88 ppm

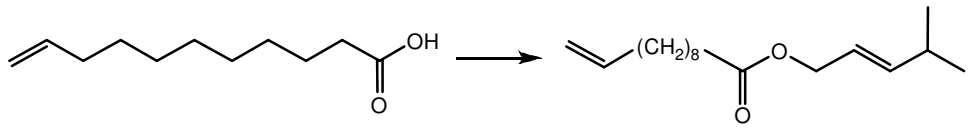
R_f 0.6 (1:1 dichloromethane:hexane)

<u>GC-MS</u>

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 10.23 minutes

Mass Spectrum (EI, Low resolution, integral with GC)

No mol ion 167 (CH_2=CH(CH_2)$_7$C=O$^+$), 149, 121, 107, 82 ((CH_3)$_2$CHCH=CH.CH$^+$)



Procedure 1: EDCI Method

To a stirred solution of undec-10-enoic acid **361** (18.4 g 0.1 mol) and *E*-4-methylpent-2-enol (12.0 g 0.12 mol) in dry dichloromethane, under nitrogen at 0°, were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (25.0 g 0.13 mol) and 4-pyrrolidino- pyridine (7 ml of 10% solution in dichloromethane) and the whole stirred for 2 hr at 0°. The clear solution was allowed to remain at ambient temperature for 1 week. The reaction was then diluted with dichloromethane, poured into ice/water, and the phases separated. The aqueous phase was then extracted with dichloromethane (2 x 50 ml), and the combined organic phases washed with 50/50 water/brine acidified with HCl to pH2 (100 ml), brine (100 ml x 2), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by chromatography (hexane/dichloromethane) to give a colourless oil. Yield 9.2 g 34%

Procedure 2. Acid Chloride Method (Recommended Method)

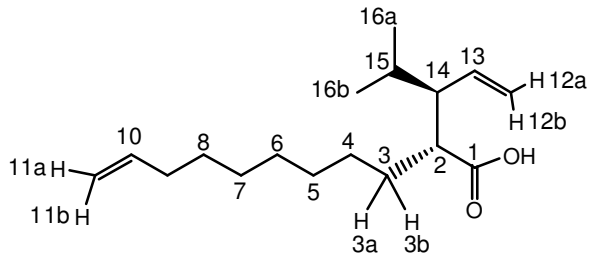
Thionyl chloride (50ml) was heated to reflux with boiled linseed oil (50 ml) for a few minutes, then fractionally distilled, the fore-run (approx 10 ml) being discarded and the fraction (approx 30 ml) distilling at 76°C (atmospheric pressure) being retained.[196]

To undec-10-enoic acid (18.4 g 0.1 mol), under nitrogen, at ambient temperature, was added thionyl chloride (prepared as above, 13.0 g, 8 ml, 0.11 mol) over 45 minutes. The solution was then heated to reflux for 2 hrs, the bulk of the excess thionyl chloride removed under reduced pressure (40°C, 20 torr), and the residue fractionally distilled (87°C, 0.23 torr, lit 102°C @ 2 torr[94]) to give the acid chloride **362**. Yield 12.59g, 62%

The acid chloride **362** (prepared as above, 12.59 g, 0.062 mol) was diluted with dry dichloromethane (5 ml) and added dropwise over 40 minutes to a stirred solution of *E*-4-methylpent-2-enol (7.4 g, 0.074 mol) and dry 2,6-lutidine (7.98 g, 0.074 mol) at 0°C. The reaction was stirred at ambient temperature for 70 hrs, diluted with dichloromethane (30 ml), washed with 2N hydrochloric acid (50 ml x 4), diluted with diethyl ether (120 ml) and washed with brine (50 ml x 6) until the washings were

perfectly neutral. The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Yield 14.78 g, 89.6% based upon the quantity of undec-10-enoyl chloride used.

(*R**)-2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoic acid **363**
(novel)



Appearance: Colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.82 (1H, ddt, J = 16.9, 10.2, 6.7 Hz, 10-H), 5.68 (1H, dt J = 17.0, 10.1 Hz, 13-H), 5.08 (1H, dd, J = 10.2, 2.2 Hz, 12a-H), 4.99 (2H, dm J = 17.0 Hz, 11b & 12b-H), 4.94 (1H, ddt, J = 10.0, 2.2, 1.2 Hz, 11a-H), 2.01 (2H, m, 9-H), 1.97 (1H, ddd, J =10.0, 7.6, 6.2 Hz, 14-H), 1.82 (1H, app octet J≈ 6.6 Hz, 15-H), 2.54 (1H, ddd, J =9.9, 7.7, 4.8 Hz, 2-H), 1.53-1.63 (1H, m, 3a/b-H), 1.44-1.54 (1H, m, 3a/b-H), 1.22-1.44 (10H, m 4,5,6,7 & 8-H), 0.95 (3H, d, J = 6.8 Hz 16a/b-H), 0.84 (3H, d, 16a/b-H),

^{13}C (125 MHz, $CDCl_3$) δ

180.23 (1-C), 139.14 (10-CH), 136.54 (13-CH), 117.52 (12-CH_2), 114.10 (11-CH_2), 53.08 (14-CH), 47.35 (2-CH), 33.74 (9-CH_2), 30.37 (3-CH_2), 29.47 (4,5,6,7 or 8-CH_2), 29.26 (4,5,6,7 or 8-CH_2), 29.01 (4,5,6,7 or 8-CH_2), 28.86 (4,5,6,7 or 8-CH_2), 27.93 (15-CH), 27.43 (4,5,6,7 or 8-CH_2), 21.42 (16a/b-CH_3), 18.28 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2926, 2855, 1702 C=O, 1640, 996, 910 vs

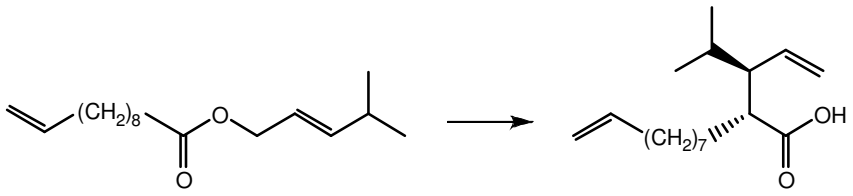
Acc Mass (ESI):

Calc: $C_{17}H_{30}O_2Na$ 289.2138

Found: 289.2138 Error: 0 ppm

R_f 0.3 (streaks) 1:1 dichloromethane:hexane

R_f 0.4 dichloromethane with 2% formic acid.



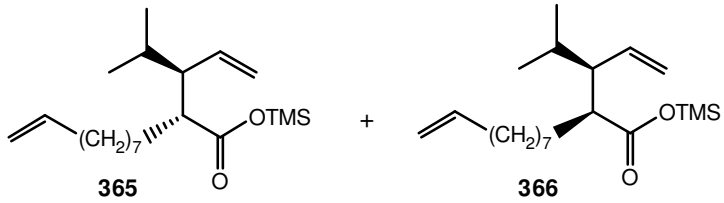
Dry DMPU (100 ml) was placed in a 500 ml flask (equipped with nitrogen purge, a large magnetic stirrer and a thermometer), cooled to -8-0°C and lithium hexamethyl-disilazide (1M solution in THF, 160 ml, 0.16 mol) added, maintaining the temperature below 0°C. This solution was then cooled to -78°C, maintaining rapid stirring. A solution of (*E*)-4-methylpent-2-enyl undec-10-enoate **360** (10.64 g 0.04 mol) in dry THF (40 ml) was then added (by syringe) over 1-2 minutes, maintaining the internal temperature below -70°C. The reaction was then stirred for a further 1.25 hrs. The cardice/acetone bath was then removed, and replaced with an empty Dewar vessel (previously cooled with cardice-acetone), the stirring adjusted so as to be as fast and stable as possible, and liquid nitrogen added to the Dewar in *small* portions, carefully bringing the internal temperature down to below -90°C, whilst maintaining brisk stirring to ensure that the solution remained fluid (albeit viscous) and did *not* freeze solid. Chlorotrimethylsilane (freshly distilled from calcium hydride *immediately* before use, 25 ml, 21.4 g 0.197 mol) was then added dropwise over 5 minutes, ensuring that it dropped directly into the solution, keeping the internal temperature below -90°C with further additions of liquid nitrogen to the cooling bath, and maintaining efficient stirring. The chlorotrimethylsilane formed a frozen upper layer on the surface of the solution. A little acetone was then added to the bath, with more liquid nitrogen, and then the temperature of the reaction was *cautiously* allowed to rise, still maintaining efficient stirring. An exotherm began at -85°, and was carefully controlled by addition of liquid nitrogen and cardice to the bath, ensuring that the internal temperature never exceeded -70°C. When the exotherm had ceased, the cooling bath was topped up with cardice, and maintained at -78°C for 1 hr. The cooling was then removed and the reaction heated to 50°C for 3 hrs. The reaction was then left at ambient temperature overnight. The reaction was then cooled to 0°C, water (100 ml) added, and concentrated hydrochloric acid added dropwise to bring the pH to 1-0. The reaction was then allowed to reach ambient temperature, adjusting the pH as necessary. The reaction was then diluted with diethyl ether (200 ml), the phases separated, and the aqueous phase extracted with further diethyl ether (3 x 100 ml), and the combined organic phases washed with brine in 100 ml portions until the washings were neutral, then dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration, and the products kept as the solution in diethyl ether.

Approximately 120 ml of *freshly regenerated* Ambersep-900-OH (96 meq at 0.8 meq per ml of wet resin[95]) previously dehydrated in dry THF, with sufficient THF to cover the resin, was placed in a small column. Approximately one third of this was then removed (as a slurry, using a wide plastic pipette), and added to the diethyl ether solution of products of the reaction, diluting with approximately 100 ml of dry THF, and stirred for approximately 20 minutes. The resin was allowed to settle, removed from the solution (pipette again) and added to the top of the column. The ether solution was then passed slowly (over 50 minutes) through the column to complete absorption of the acid. The column was then washed through with dry THF (200 ml), dichloromethane (200 ml), THF (100 ml) and the column allowed to drain. Formic acid (35 ml) was then diluted to 350 ml with dry THF. The column was then filled with this solution, and the rest of the solution used to elute the column to complete the release of the product. The total volume of eluent was then concentrated under reduced pressure at about 40°, adding and evaporating several changes of approximately 50 ml of toluene to effect azeotropic removal of the formic acid, and then several changes of dichloromethane to remove the toluene. The residue was dissolved hexane/dichloromethane, filtered to remove a small amount of gummy material, and the solvent removed under reduced pressure. 5.79 g, 54.4% of crude product DR 6.4:1 (by NMR).

The title compound **363** was separated from the minor isomer **364** and the persistent impurity (**367** which runs marginally faster than the acids) by repeated chromatography, retaining fractions of acceptable DR, and combining and subjecting those of unacceptable DR to further chromatography. In all cases, the column was packed with a slurry of silica in 15% dichloromethane in hexane, and the sample loaded. The proportion of dichloromethane was increased to 20%, and this concentration used until all the impurity **367** had been eluted, and continued until elution of the acid commenced. At this point, the first few fractions (the title compound elutes marginally faster than the minor isomer) were collected individually, and the concentration of dichloromethane increased as rapidly as practical (due to exothermic adsorption) to 100% in order to ‘strip’ the column.

In this manner four batches were obtained from this reaction 2.2 g (DR 10.4:1) 1.25g (DR 6.6:1), 0.87 g (DR 4.3:1), and 0.3 g (DR 1.6:1)

(*R**)-trimethylsilyl 2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoate **365** and
(*S**)-trimethylsilyl 2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoate **366**
(novel)



365 **366**

Mixture of isomers

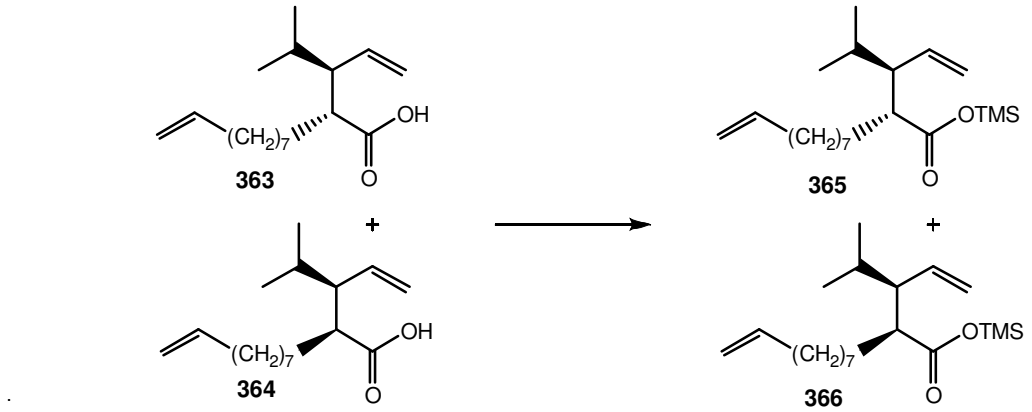
These compounds were not fully characterized. They were prepared solely as a mixture in dilute solution for GC analysis

GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal.

Retention Time **365** 10.33 minutes
Mass Spectrum (EI, Low resolution, integral with GC)
338 (M^+), 323, 295, 213, 171, 73 (Me_3Si^+)

Retention Time **366** 10.28 minutes
Mass Spectrum (EI, Low resolution, integral with GC)
323, 295, 213, 171, 73 (Me_3Si^+)



Approximately 3 mg of an 8.1:1 mixture of (*R**)-2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoic acid **363** and (*S**)-2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoic acid **364**, mixture was dissolved in approx 0.5 ml of dichloromethane in a 2 ml GC sample vial, which was then sealed with a septum. Approximately 0.5 ml of 'silylating solution' (see preparation of **337**) was added *via* syringe and left at ambient temperature for 1 week. The solution was used directly as a GC sample, showing the title compounds and excess BSTFA.

Pre-treatment/Regeneration of Ambersep-900-OH.

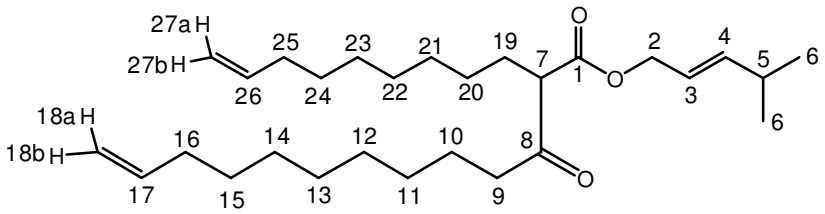
Approximately 120 ml of Ambersep-900-OH (damp, as supplied*) was washed *by decantation* with several changes of approximately 200 ml de-ionized water, decanting the cloudy supernatant liquid as soon as the resin beads had settled, in order to remove suspended fines. The resin was then suspended in approximately 100 ml of 2N hydrochloric acid, placed in a column, eluted with further 2N hydrochloric acid (200 ml) then with deionised water until the washings were neutral. The resin was kept covered by the eluent, and occasionally agitated (wide pipette) in order to remove bubbles and to ensure that the resin (which expands and contracts during treatment) was still 'free-flowing'. The column was then eluted with 10% potassium hydroxide solution (400 ml in total), the first portions (approximately 50 ml) being added slowly, carefully, with agitation of the resin and dilution/elution with deionized water as necessary, as this process is exothermic. This exotherm ceased once the whole of the resin had changed from cream to pale-pink, and the remainder of the hydroxide solution was passed through the resin over approximately 1 hr, then washed with deionised water until the washings were neutral. The column was then eluted with methanol (400 ml), and then dry THF** (400 ml), then kept under THF in a sealed container until required for use, the THF being replaced by fresh before actual use.

Note:-

* This describes the pre-treatment for fresh resin, which is supplied damp, already in hydroxide form. The same preparation was used for regenerating used resin from the formate form left by the formic acid. Once in hydroxide form, the resin readily absorbs carbon dioxide from the air. The material as supplied therefore contains an unknown proportion in carbonate form, which may affect absorption, and creates bubbles when displaced. It is for this reason that the resin is first put into chloride form by the large excess of hydrochloric acid, which displaces hydroxide, carbonate and formate. Elution with potassium hydroxide regenerates the resin in carbonate-free hydroxide form, hence the stipulation '*freshly regenerated'.*

** The specification *dry* THF should also be noted. Absolute dryness is not actually necessary, however commercial THF contains a trace of 2,6-di(*t*-butyl)4-methylphenol (*aka* BHT 'butylated hydroxy toluene') as a stabilizer. The drying process used (distillation from sodium/benzophenone) very effectively removes this material in addition to drying the solvent.

(*E*)-4-methylpent-2-enyl 2-(non-8-enyl)-3-oxotridec-12-enoate **367**
(novel)



Appearance: Colourless resin

This material was an impurity isolated during the purification **363**, therefore no details of preparation are given.

^{1}H NMR (500 MHz, $CDCl_3$) δ
5.71-5.87 (3H, m, 17,26 & 4-H), 5.50 (1H, dt, J = 15.5, 6.5 Hz, 3-H), 5.0 (2H, bd, J = 17.0, 18a & 17a-H), 4.94 (2H, bd, J = 10.1, 18b & 27b-H), 4.57 (1H, d, J = 6.5 Hz, 2-H), 3.42 (1H, t, J = 7.3 Hz, 7-H), 2.54 (1H, part of ABX_2 system, J = 17.3, 7.3 Hz 9a-H), 2.47 (1H, part of ABX_2 system J = 17.3, 7.3 Hz 9b-H), 2.24-2.39 (1H, m, 5-H), 2.04 (4H, m, 16 & 25-H), 1.76-1.9 (2H, m, 19-H), 1.5-1.62 (2H, m, 10-H), 1.34-1.44 (4H, m, 24 & 15-H), 1.24-1.34 (16H, m, 11,12,13,14,21,20,22 & 23-H), 1.00 (6H, d, J = 6.8 Hz, 6-H)

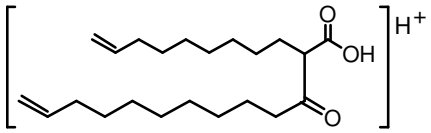
^{13}C (125 MHz, $CDCl_3$) δ
205.38 (8-C), 169.78 (1-C), 143.88 (4-CH), 139.12 (17 or 26-CH), 139.09 (17 or 26-CH), 120.39 (3-CH), 114.13 (18 or 27-CH_2), 114.11 (18 or 27-CH_2), 65.98 (2-CH_2), 59.24 (7-CH), 41.75 (9-CH_2), 33.75 (16 or 25-CH_2), 33.72 (25 or 16-CH_2), 30.74 (5-CH), 29.30 (11-14, 20-23-CH_2), 29.27 (11-14, 20-23-CH_2), 29.14 (11-14, 20-23-CH_2), 29.04 (11-14, 20-23-CH_2), 29.03 (11-14, 20-23-CH_2), 28.96 (11-14, 20-23-CH_2), 28.84 (11-14, 20-23-CH_2), 28.20 (19-CH_2), 21.96 (6-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2925 (vs), 855 (s),1742 C=O (vs), 714 C=O (vs),1640 C=O enol 1463, 1165, 1055 (s), 1033, 995, 972, 908 (vs), 722, 632

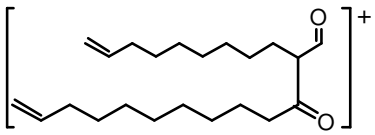
Acc Mass (ESI):
Calc: $C_{28}H_{48}O_3Na$ 455.3496
Found: 455.3503 Error: -1.62 ppm
R_f 0.4 (dichloromethane + 2% formic acid)

Mass Spectrum EI, Low resolution

433 (MH+) 333 (see below), 350 (see below), 306, 226



Mass 350



Mass 333

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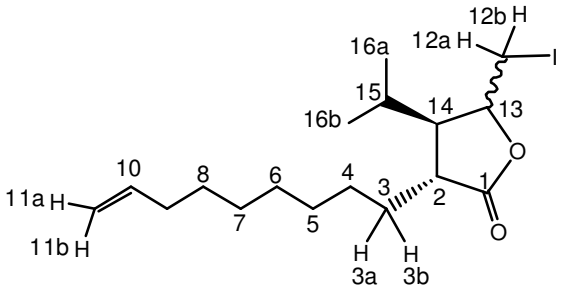
(3*R**,4*R**)-5-(Iodomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one **368** (novel)



Appearance: Brown resin

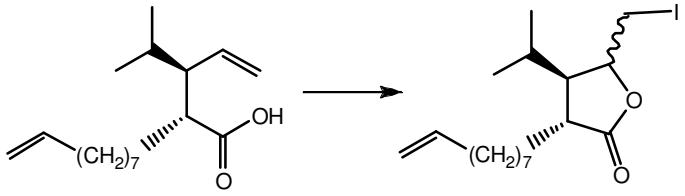
Note that this material consists of approximately 90% of one isomer (at 13-C) and 10% of the other isomer. Further separation was not attempted given the instability of this compound. The assignations given are those of the major isomer. No attempt was made to determine the stereochemistry at 13-C by NOE. See separation of the analogous bromolactone **387** into its isomers **388** and **389** for details of this procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ
5.81 (1H, ddt, J = 17.0, 10.0, 6.8 Hz, 10-H*), 4.99 (1H, dd, J = 17.0, 2.0, 11b-H), 4.93 (1H, bd, J = 10.0 Hz, 11a-H), 4.70-4.76 (1H, app q, J ≈ 6.8 Hz, 13-H), 3.41 (1H, part of ABX system, J = 10.3, 6.6, 12a-H*), 3.34 (1H, part of ABX system, J = 10.3, 7.6, 12b-H*), 2.50 -2.57 (1H, m, 2-H), 2.18-2.24 (1H, m, 14-H), 2.01-2.11 (3H, m, 15 & 9-H), 1.67-1.78 (1H, m, 3a-H), 1.57-1.66 (1H, m, 3b-H), 1.2-1.45 (10H, m, 4,5,6,7 & 8-H), 0.94 (3H, d, J = 7.0 Hz, 16a/b-H), 0.96 (3H, d, J = 7.0 Hz, 16a/b-H)

^{13}C (125 MHz, $CDCl_3$) δ
178.54 (1-C), 139.05 (10-CH), 114.17 (11-CH_2), 80.69 (13-CH), 48.12 (2-CH), 42.64 (14-CH), 33.70 (9-CH_2), 30.23 (3-CH_2), 29.3 (4,5,6,7 or 8-CH_2), 29.19 (4,5,6,7 or 8-CH_2), 28.97 (4,5,6,7 or 8-CH_2),28.82 (4,5,6,7 or 8-CH_2), 27.13 (4,5,6,7 or 8-CH_2), 25.63 (15-CH), 21.56 (16a/b-CH_3), 18.41 (16a/b-CH_3), 0.76 (12-CH_2)

IR (thin film, ν_{max} cm^{-1}) 2926, 2854, 1777 C=O, 1465, 1167

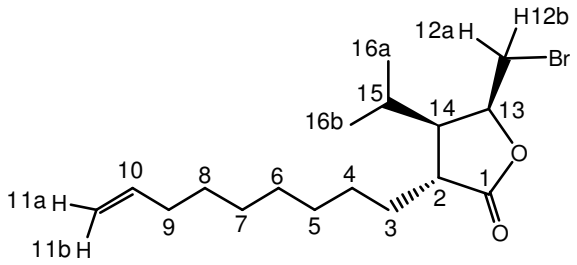
Acc Mass (ESI):
Calc: $C_{17}H_{30}O_2I$ 393.1285 $(MH)^+$
Found: 393.1285 Error: -0.22
R_f 0.7 (dichloromethane)



Method based upon that of House.[105]

(*R**)-2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoic acid **363** (1.33 g, 0.005 mol) was dissolved in THF (20 ml), and sodium hydrogen carbonate (0.21 g, 0.0025 mol), potassium iodide (0.83 g, 0.005 mol), water (20 ml), and iodine (3.175 g, 0.0125 mol) were added. The reaction was stirred under nitrogen at ambient temperature for 5 hrs. The reaction was then diluted with saturated sodium hydrogen carbonate (100 ml) extracted with diethyl ester (4 x 100 ml), the combined organic phases washed with brine (5 x 30 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. TLC indicated two close-running major products (the two isomers of the iodolactone), plus minor impurities. The material was purified by chromatography (using hexane /dichloromethane as eluent). The products were left at ambient temperature overnight in solution. There was evidence of decomposition. The fractions were combined and the solvent removed under reduced pressure, to give two fractions, one fraction containing mainly the higher-running isomer (0.475 g, 24%, see comments NMR spectrum on previous page) and the other (0.80 g, 41%) a mixture of isomers. Product kept in freezer prior to use.

(3*R**,4*R**,5*S**)-5-(bromomethyl)-4-isopropyl-3-(non-8-enyl) dihydrofuran-2(3H)-one **388** (novel)



Appearance: Colourless resin

(Isolated from mixture of isomers **387**)

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.80 (1H, ddt, J = 17.0, 10.3, 6.7 Hz, 10-H), 4.99 (1H, dd, J = 17.0, 1.6 Hz, 11b-H), 4.93 (1H, d, J = 10.3 Hz, 11a-H), 4.74 (1H, app q, J = 6.5 Hz, 13-H), 3.60 (1H, part of ABX system, J = 10.2, 6.1 Hz, 12a-H), 3.59 (1H, part of ABX system, J = 10.2, 6.4 Hz, 12b-H), 2.54 (1H, dt, J = 6.5, 5.4 Hz, 2-H), 2.21 (1H, app dt, J = 6.8, 5.2 Hz, 14-H), 2.93 (3H, m, 15 & 9-H), 1.67 (2H, m, 3-H), 1.2-1.5 (10H, m, 4,5,6,7 & 8-H), 0.97 (3H, d, J = 7.5, 16a/b-H), 0.95 (3H, d, J = 7.5 Hz, 16a/b-H)

For NOE study to prove relative stereochemistry of C-14 and C-13 , see page 177

^{13}C (125 MHz, $CDCl_3$) δ

178.51 (1-C), 139.05 (10-CH), 114.16 (11-CH_2), 79.55 (13-CH), 48.04 (14-CH), 42.53 (2-CH), 33.70 (9-CH_2), 30.38 (3-CH_2), 29.46 (4,5,6,7 8 or 12-CH_2), 29.34 (4,5,6,7 8 or 12-CH_2), 29.19 (4,5,6,7 8 or 12-CH_2), 28.97 (4,5,6,7 or 8-CH_2), 28.82 (4,5,6,7 or 8-CH_2), 26.91 (4,5,6,7 or 8-CH_2), 26.02 (15-CH), 21.71 (16a/b-CH_3), 18.87 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2965, 29`30, 2856, 1777 C=O 1469, 1179, 1026

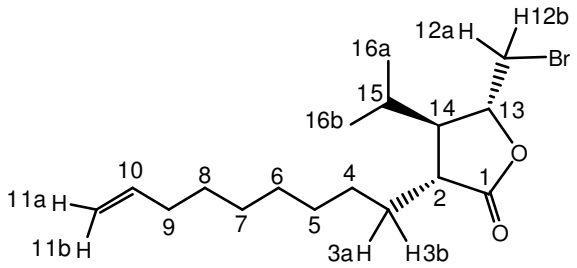
Acc Mass (ESI):

Calc: $C_{17}H_{29}O_2BrNa$ 367.1243

Found: 367.1253 Error: -2.59 ppm

R_f 0.7 (dichloromethane)

(3*R**,4*R**,5*R**)-5-(bromomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one **389** (novel)



Appearance: Colourless resin

(Isolated from mixture of isomers **387**)

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.80 (1H, ddt, J = 17.2, 10.2, 6.5 Hz, 10-H), 4.99 (1H, d, J = 17.2 Hz, 11b-H), 4.92 (1H, d, J = 10.2 Hz, 11a-H), 4.37 (1H, app q, J = 5.1 Hz, 13-H), 3.59 (1H, part of ABX system, J = 11.1, 4.7 Hz, 12a-H), 3.48 (1H, part of ABX system, J = 11.2, 5.0 Hz, 12b-H), 2.43 (1H, app q, J = 6.6 Hz, 2-H), 2.04 (1H, m, 9 & 14-H), 1.75-1.85 (2H, m, 15 & 3b-H), 1.6-1.7 (1H, m, 3a-H), 1.25-1.55 (10H, m, 4,5,6,7 & 8-H), 0.98 (12H, d, J = 6.8 Hz, 16a/b-H)

For NOE study to prove relative stereochemistry of C-2, C-14 and C-13 see page 174.

^{13}C (125 MHz, $CDCl_3$) δ

178.12 (1-C), 139.07 (10-CH), 114.15 (11-CH_2), 79.30 (13-CH), 49.62 (14-CH), 43.17 (2-CH), 34.93 (12-CH_2), 33.70 (9-CH_2), 31.96 (3-CH_2), 30.80 (15-CH), 29.43 (4,5,6,7 or 8-CH_2), 29.18 (4,5,6,7 or 8-CH_2), 28.98 (4,5,6,7 or 8-CH_2), 28.86 (4,5,6,7 or 8-CH_2), 28.83 (4,5,6,7 or 8-CH_2), 19.59 (16a/b-CH_3), 19.50 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2930, 2859, 1777 C=O vs, 1172, 1059 vs, 1034 vs, 1013 s

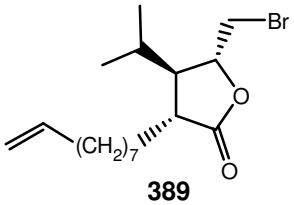
Acc Mass (ESI):

Calc: $C_{17}H_{29}O_2Na$ 367.1243

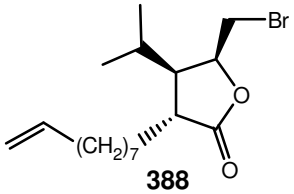
Found: 367.1255 Error: -3.33

R_f 0.6 (dichloromethane)

NOE Study of **388** and **389**



389



388

Samples of the bromolactones **388** and **389,** separated by chromatography, were examined by Nuclear Overhauser Effect (NOE) spectroscopy (NOESY) to determine their configurations. The results are tabulated below.

389	2	3	12	13	14	15
3	✓					
12	✗	✓				
13	✓	?	✓			
14	✓	✓	✓	✓		
15	?	?	✓	✓	?	
16	✓	✓	✓	✓	✓	✓

Correlations in **389**

388	2	3	12	13	14	15
3	✓					
12	✓	✗				
13	✓	✓	✓			
14	✓	✓	✓	✓		
15	✗	✗	✓	✗	?	
16	✓	✓	✓	✓	✓	✓

Correlations in **388**

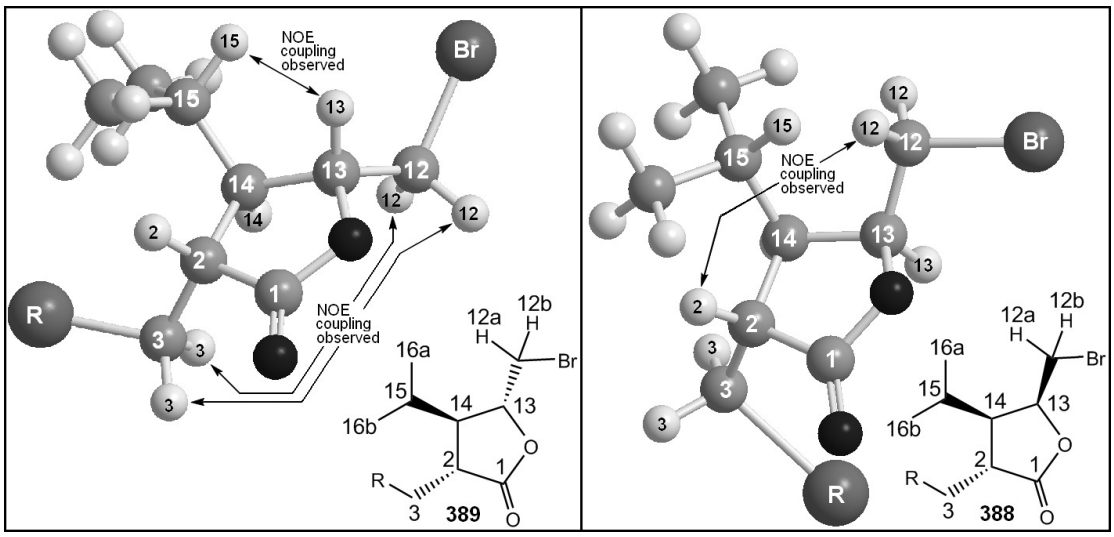
✓= Correlation observed
✗ = No correlation observed
? = Not determinable due overlap of signals, or signals being too close to diagonal etc

Comparing the two sets of results, the key observable differences between the two isomers are:-

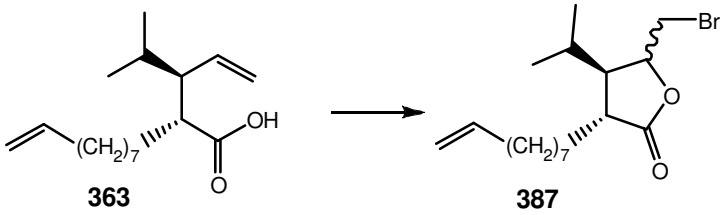
389		**388**	
12,3	Correlation	12,3	No Correlation
12,2	No Correlation	12,2	Correlation
15,13	Correlation	15,13	No Correlation

3D representations of **388** and **389**, with the NOE interactions marked are shown overleaf. These are consistent with, and therefore confirm, the structures above.

It should be noted that the conformations shown are not minimum energy conformations. They are the conformations implied by the correlations observed.



(3R,4R)-5-(Bromomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one **387**
(mixture of **388** and **389**)



363 **387**

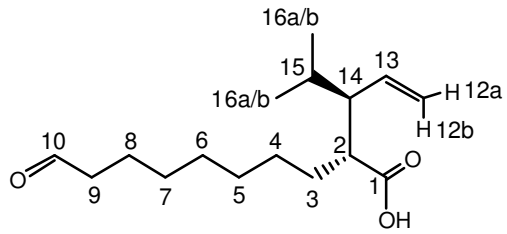
Method of Ohfune and co-workers,[125] modified by use of dichloromethane rather than THF as solvent, and workup using Sn^{2+} bound upon Amberlyst-15 resin[91] to reduce excess N-bromosuccinimide.

Amberlyst-15 (dry, as supplied, in H^+ form)[197] 10 g (0.047 equivalents based upon 4.7meq/g of dry resin) was washed (by decantation, to remove fines) with several changes of deionized water, then placed in a column. Tin (II) chloride dihydrate (11.25 g, 0.05 mol) was dissolved in deionized water, filtered to remove the slight precipitate, then the solution passed through the resin over approximately 20 minutes. The column was then eluted with deionized water until neutral, then the resin dehydrated by elution with dry THF (120 ml), then 100 ml dichloromethane, then set aside, covered with dichloromethane.

(*R**)-2-((*S**)-4-Methylpent-1-en-3-yl)undec-10-enoic acid **363** was dissolved in dichloromethane (300 ml), cooled to 0°C, and N-bromosuccinimide (3.09 g, 0.0174 mol), previously recrystallized from water and dried *in vacuo* at 30°C) added. The reaction was stirred at 0°C for 20 minutes, then at ambient temperature for 4 hrs, until no starting material could be observed by TLC. The previously-prepared resin was then added and the whole stirred at ambient temperature for 20 minutes until KI/starch paper indicated that no further N-bromosuccinimide was present. The resin was then removed by filtration, washed with dichloromethane and the solvent removed under reduced pressure. Chromatography using neat dichloromethane as eluent gave 3.57 g (71%) of mixed isomer product 387.

A sample of **387** was separated by chromatography using hexane/dichloromethane as eluent into the two isomers **388** and **389**.

(*R**)-2-((*S**)-4-methylpent-1-en-3-yl)-10-oxodecanoic acid **405**
(novel)



This compound was not obtained pure, and is not fully characterized. Its susceptibility to oxidation (to the diacid **409**) and dimerization (to **408**) are discussed in 2.3.2.4. The spectral details presented are derived from a sample 64% of **409**, 33% of **405** and 3% of **408**. The degree of similarity of the spectra (given that the portions of the molecules 1-C to C-8 and 12-C to 16-C are identical) should be noted. The details presented should therefore be treated with a degree of caution.

^{1}H NMR (500 MHz, $CDCl_3$) δ
9.75 ('1H'*, t, J = 1.9 Hz, 10-H), 5.67 (1H, dt, J= 17.0, 10.1 Hz, 13-H), 5.07 (1H, dd, J = 10.31, 2 Hz, 12a-H), 4.98 (1h, dd, J = 17.0, 1.9 Hz, 12b-H), 2.47-2.57 (1H, m, 2-H), 2.41 (1H, td, J = 7.3, 1.9 Hz, 9-H), 1.93-2.02 (1H, m, 14-H), 1.75-1.84(1H, m, 15-H), 1.20-1.65 (12H, m, 3,4,5,6,7 & 8-C), 0.95 (3H, d, J = 6.6 16a/b-H), 0.81 (3H, d, J = 6.6 Hz, 16a/b-H)

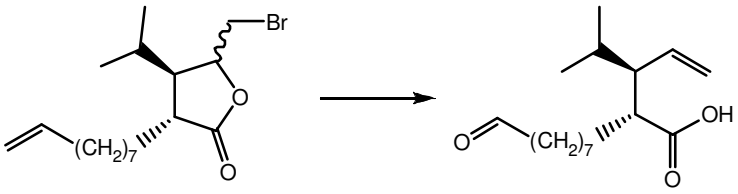
(* integrates 0.34, consistent with 33% of compound in mixture)

^{13}C (125 MHz, $CDCl_3$) δ
202.82 (10-CHO), 180.75 (1-C), 136.51 (13-CH), 117.52 (13-CH), 53.09 (14-CH), 47.39 (2-CH), 43.83 (9-CH_2), 30.31 (3-CH_2), 29.28 (4,5,6,7 or 8-CH_2), 29.11 (4,5,6,7 or 8-CH_2), 29.03 (4,5,6,7 or 8-CH_2), 27.94 (15-CH), 27.34 (4,5,6,7 or 8-CH_2), 22.00 (4,5,6,7 or 8-CH_2), 21.41 (16a/b-CH_3), 18.3 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2927, 2856, 1703 C=O broad), 1639, 914 vs

Rf 0.5 (dichloromethane + 1% formic acid)

Acc Mass (ESI):
Calc: $C_{16}H_{28}O_3Na$ 291.1931
Found: 291.1937 Error: 2.18 ppm
(Note that 307.1887 **409**, and 541.3881 **408** were also present.



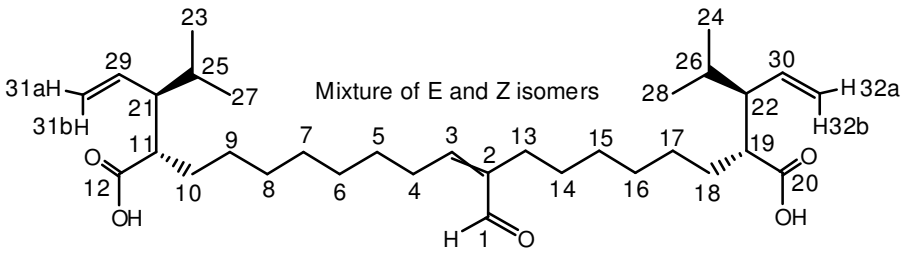
The following precautions were adopted for ozonolysis reactions. No grease was used on the joints, the inlet and outlet tubes were passed through appropriately arranged Dreschel bottles (in order to prevent reaction mixture being drawn into the ozonizer, or absorption solution being drawn into the reaction. The outgoing gas was passed through a 'funnel trap' containing strong sodium metabisulfite solution in order to remove ozone. All operations with ozone were conducted with the apparatus behind a blast screen, the blast screen being removed after only reduction of the ozonide by triphenylphosphine.

In a 100 ml 3-necked flask, equipped with a thermometer, magnetic stirrer, and two gas ports,(3*R**,4*R**)-5-(Bromomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one **387** (0.12 g, 0.00034 mol) was dissolved in dichloromethane (40 ml), the flask purged with nitrogen, and cooled to -78°C. Ozonized oxygen was then passed through the solution until (4 hrs) it had assumed a definite blue colour indicating excess ozone in solution. A precipitate was observed. Nitrogen was then passed (still at -78°C) for a further 1h to purge the ozone, then triphenylphosphine (0.234 g 0.00089 mol) and a further 10 ml of dichloromethane added. The reaction was stirred at -78° for 1h, then allowed to warm to 0-10°C (ice bath) and the now-clear solution left overnight at ambient temperature.

A 100ml flask was charged with isopropanol (50 ml), water (5 ml) and zinc dust (2 g), and heated to 50-60°C with stirring, and a very slow nitrogen purge. The solution from the ozonolysis was then added dropwise over 30 minutes, allowing the dichloromethane to evaporate. Some isopropanol evaporated under these conditions, the flask was topped up to its original level with further isopropanol, a reflux condenser fitted, and the reaction heated to just below reflux for 7 hrs, then left at ambient temperature overnight. The zinc was then removed by filtration, washing through with further isopropanol, then the solvent removed under reduced pressure. To the residue was then added water (5 ml) and one drop of concentrated hydrochloric acid to bring the pH to 1. This was then extracted with diethyl ether (3 x 15 ml), the combined

organic phases washed with brine (10 ml x 3), and the solution dried over anhydrous sodium sulfate. This solution was then passed over 20 minutes through a column of 4 ml Ambersep-900-OH (freshly regenerated and dehydrated with THF), washing through with dry THF. The acidic products were then released from the resin by eluting with 10% formic acid in dry THF (20 ml) washing the resin through with more dry THF. The solvent was then removed under reduced pressure, adding and removing toluene (4 x 30 ml), chloroform (4 x 30 ml). Product 60 mg, approx 65% (product known to be a mixture)

(2*R**,18*S**)-9-formyl-18-((*R**)-4-methylpent-1-en-3-yl)-2-((*S**)-4-methylpent-1-en -3-yl)nonadec-9-enedioic acid **408**
(novel)



Appearance: Colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

9.36 (1H, s, 1-H), 6.44 (1H, t, J = 7.3 Hz, 3-H), 5.69 and 5.66 (2H, overlapping (ddd, J = 17.1, 10.2, 10.2 Hz) & (ddd, J = 17.1, 10.2, 10.2 Hz) 29 & 30-H), 5.08 (2H, app dt J = 10.3, 2.5 Hz, 31a & 32a-H), 4.99 (2H, bd, J = 17.1 Hz, 31b & 32b-H), 2.45-2.60 (2H, m, 19 & 11-H), 2.33 (2H, app q, J = 7.3 Hz, 4-H), 2.16-2.26 (2H, m, 13-H), 1.92-2.02 (2H, m, 22 & 22-H), 1.75-1.88 (2H, m, 25 & 26-H), 1.23-1.65 (22H, m, 5,6,7,8,9,10,14,15, 16,17 & 18-H), 0.94 (6H, d, J = 6.7 Hz, 23 & 24-H), 0.82 (6H, d, J = 6.7 Hz, 27 & 28 H)

^{13}C (125 MHz, $CDCl_3$) δ

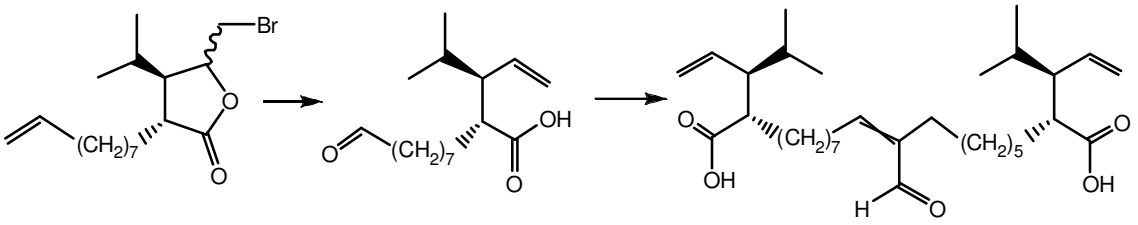
195.27 (1-CHO), (181.94, 181.91, 181.88) (12*E/Z* or 20*E/Z*-C*), 155.48 (3*E/Z*-CH), 155.44 (3*E/Z*-CH), 143.77 (2*E/Z*-C), 143.74 (2*E/Z*-C), (136.43, 136.39, 136.33 (29*E/Z* or 30*E/Z*-CH**), (117.59, 117.57, 117.55, 117.54) (31*E/Z* or 32E/Z-CH_2), 53.12 (21 or 22-CH), 53.09 (21 or 22-CH), (48.08, 48.01, 47.72, 47.66) (11*E/Z* or 19*E/Z*-CH), (30.61, 30.56, 30.50, 30.44, 29.67, 29.60, 29.34, 29.29, 29.12, 28.99, 28.97) 5-10*E/Z* or 14-18*E/Z*-CH_2***), (28.69, 28.67, 28.66, 28.66) (4-10*E/Z* or 14-18*E/Z*-CH_2***), (28.48, 28.45, 28.29, 28.25, 27.95) (5-10*E/Z* or 14-18*E/Z*-CH_2***), (27.83, 27.81, 27.79, 27.77) (25*E/Z* or 26*E/Z*-CH), (27.52, 27.46, 27.39, 27.35) (5-10*E/Z* or 14-18*E/Z*-CH_2***), 24.04 (13*E/Z*-CH_2), 24.00 (13*E/Z*-CH_2), ((21.452, 21.450, 21.43, 21.42) (23*E/Z* or 24 E/Z-CH_3), (18.31, 18.05, 17.94, 17.84) (27*E/Z* or 28*E/Z*-CH_3)

* only 3 of the 4 signals could be resolved
** only 3 of the 4 signals could be resolved
*** only 20 of the 24 signals could be resolved

IR (thin film, ν_{max} cm^{-1}) 3888 (b, OH), 2936, 1772 C=O (s),1720 C=O (vs), 1461, 1372, 1167 (s), 1033 (vs), 991, 920

Acc Mass (ESI):
Calc: $C_{32}H_{54}O_5Na$ 541.3863
Found: 541.3872 Error: 1.58 ppm

R_f 0.1 (9:1 dichloromethane:ethyl acetate)



See preparation of **405** *for precautions with ozonolysis reactions*

(3*R**,4*R**)-5-(Bromomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one_**387** (0.93 g, 0.00269 mol) was dissolved in dichloromethane (100 ml), the flask purged with nitrogen, then cooled to -78°C. Ozonized oxygen was then passed through the solution until (1.5 hr) it had assumed a definite blue colour. Nitrogen was then passed (maintaining the temperature -78°C) for a further 1 hr to purge the ozone, then triphenylphosphine (1.55 g 0.00592 mol) added. The reaction was stirred at -78°C for 20 minutes, then stirred at ambient temperature overnight.

The dichloromethane was then removed in a stream of nitrogen at 40°C, then isopropanol (100 ml), water (10 ml) and zinc dust (5.0 g) added, and the whole heated to 60-70°C for 3 hrs, after which time TLC indicated complete reaction. The zinc was removed by filtration, washing through with further isopropanol, then the solvent removed under reduced pressure. To the residue was then added brine (50 ml), diethyl ether (50 ml) and the aqueous phase acidified to pH to 1 with a few drops of concentrated hydrochloric acid. This was then extracted with diethyl ether (3 x 50 ml), the combined organic phases washed with brine until the washings were neutral, and the solution dried over anhydrous sodium sulfate. This solution was then passed over 20 minutes through a column of 20 ml Ambersep-900-OH (freshly regenerated and dehydrated with THF), washing through with dry THF. The acidic products were then released from the resin by eluting with 10% formic acid in dry THF (40 ml) washing through with more dry THF. The solvent was then removed under reduced pressure, then adding and removing under reduced pressure, toluene (4 x 30 ml), chloroform (4 x 30 ml). The residue was dissolved in THF. One third of this was used for further experiments, the remaining two thirds (containing at least 3 products) were subjected to chromatography (dichloromethane/hexane). The only identifiable compound was **408** 32 mg, 6.8%.

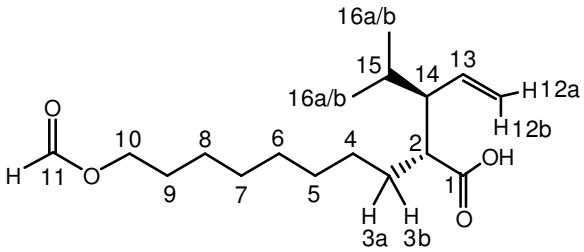
Zinc Borohydride Solution 0.1M

Method of Paquette[198] with modifications.

Anhydrous zinc chloride was prepared[199] as follows:-
Approximately 7.0 g of anhydrous zinc chloride was quickly powdered with minimal exposure to air. This was then heated with thionyl chloride to 70°C (just below reflux) for 5 hrs, with a slow nitrogen purge. The bulk of the thionyl chloride was then removed by distillation, the remainder by purging the flask at 100°C with dry nitrogen for 1 hr. The residue was transferred to a dry flask, and placed overnight in a desiccator *in vacuo* over fresh potassium hydroxide.

Anhydrous zinc chloride (prepared as above) (1.24 g, 0.0091 mol) was dissolved in dry diethyl ether (91 ml) under nitrogen, then cooled to 0°C. Sodium borohydride (0.168 g 0.018 mol) was then added *en masse* and stirred overnight at 0°C. The solution was kept under nitrogen.

(*R**)-10-(formyloxy)-2-((*S**)-4-methylpent-1-en-3-yl)decanoic acid **410**
(novel)



Appearance: colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

8.06 (1H, s, 11-H), 5.68 (1H, ddd, J = 17.0, 10.0, 7.0 Hz, 13-H), 5.08 (1H, dd, J = 10.3, 2.2 Hz, 12-H), 4.99 (1H, dd, J = 17.1, 2.2 Hz, 12b-H), 4.16 (2H, t, J = 6.7 Hz, 10-H), 2.54 (1H, ddd, J = 9.8, 7.8, 4.8 Hz, 2-H), 1.97 (1H, ddd, J = 10.0, 7.8, 6.2 Hz, 14-H), 1.82 (1H, app oct, J ≈ 6.6 Hz, 15-H), 1.66 (1H, app quint, J ≈ 6.8 Hz, 9-H), 1.54-1.62 (1H, m, 3a-H), 1.44-1.54 (1H, m, 3b-H), 1.25-1.60 (10H, m, 4,5,6,7 & 8-H), 0.95 (3H, d, J = 6.7 Hz, 16a/b-H), 0.83 (3H, d, J =6.7 Hz, 16a/b-H)

^{13}C (125 MHz, $CDCl_3$) δ

180.07 (1-C), 161.18 (11-CHO), 136.55 (13-CH), 117.52 (12-CH_2), 64.07 (10-CH_2), 53.10 (14-CH), 47.35 (2-CH), 30.36 (3-CH_2), 29.38 (4,5,6,7 or 8-CH_2), 29.23 (4,5,6,7 or 8-CH_2), 29.04 (4,5,6,7 or 8-CH_2), 28.47 (9-CH_2), 27.95 (15-CH), 27.39 (4,5,6,7 or 8-CH_2), 25.74 (4,5,6,7 or 8-CH_2), 21.43 (16a/b-CH_3), 18.29 (16a/b-CH_3)

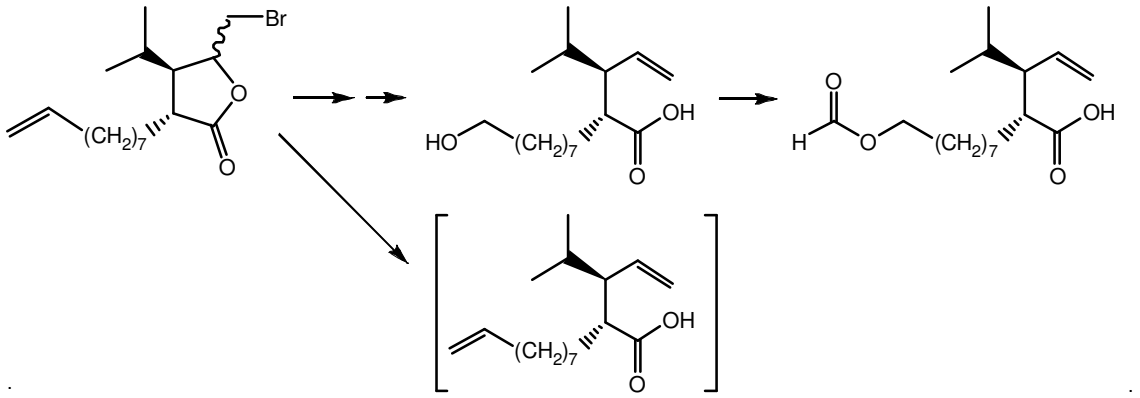
IR (thin film, ν_{max} cm^{-1}) 2927, 2855, 1729 (C=O formyl), 1704 (C=O carboxyl), 1464, 1180

Acc Mass (ESI):

Calc: $C_{17}H_{30}O_4Na$ 321.2036

Found: 321.2034 Error: -0.72 ppm

R_f 0.2 (dichloromethane +1% formic acid)

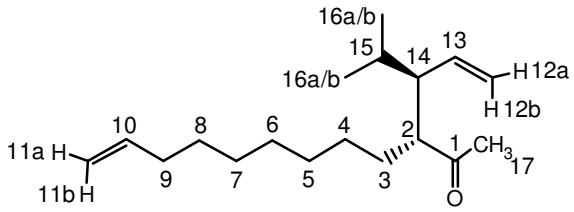


See preparation of **405** *for precautions with ozonolysis reactions.*

(3*R**,4*R**)-5-(Bromomethyl)-4-isopropyl-3-(non-8-enyl)dihydrofuran-2(3H)-one_**387** (0.755g, 0.00219 mol) was dissolved in dichloromethane (120ml), the flask purged with nitrogen, then cooled to -78°C. Ozonized oxygen was then passed through the solution until it had assumed a definite blue colour (2 hrs), and for 45 minutes thereafter. Oxygen was then passed through the solution, then nitrogen (maintaining the temperature at -78°C throughout) for a further 1 hr to purge the ozone, then triphenylphosphine (1.14 g 0.00437 mol) added. The reaction was stirred at -78°C for 1 hr, then stirred at ambient temperature overnight. The solvent was then removed under reduced pressure at 40°C, and two changes of 40 ml dry diethyl ether added and removed. The residue was dissolved/suspended in dry diethyl ether, cooled to -78°C and zinc borohydride solution (made up the day before, 0.1 M, 40 ml, 0.04 mol) added over 2 minutes, with brisk stirring. The reaction was stirred at -78°C for 2 hrs, allowed to warm to 0°, stirred for a further 1 hr. Water (2 ml) was then added, with vigorous stirring, followed by more water (5 ml) and a few drops of glacial acetic acid to bring the pH to 3. The reaction was washed with brine (3 x 30 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. isopropanol (90 ml) water (9 ml) and zinc dust (3.0 g) were then added, and the whole heated to 70°C for 1h, left at ambient temperature overnight, then heated to 70°C for 3 hrs. The zinc was then removed by filtration, washing through with further isopropanol, and the solvent removed under reduced pressure. The residue was then partitioned between brine (30 ml) and diethyl ether (100 ml) and the aqueous phase acidified to pH1 with a few drops of concentrated hydrochloric acid. The phases were separated, the aqueous phase extracted with further diethyl ether (2 x 100 ml), washed with brine (3 x 30 ml) and the solution dried over anhydrous sodium sulfate. The solution was then passed through a column of freshly regenerated Ambersep-900-OH (20 ml, dehydrated with THF) over

20 minutes, washing through with dry THF. The acidic products were released with 10% formic acid in THF (40 ml), washed through with further THF, and the solvent removed under reduced pressure. The products were separated by chromatography, using dichloromethane with 1% formic acid as eluent. Two products were obtained, the title compound **410**, 0.2 g, 30% and **363**, 40 mg 7%), the presence of **363** indicating that the ozonolysis had been incomplete.

(*R**)-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **421**
(novel)



Appearance: Colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.81(1H, ddt, J = 17.03, 10.3, 6.6 Hz,10-H), 5.57 (1H, ddd, J = 17.2, 10.2, 7.0 Hz, 13-H), 5.06 (1H, dd, J = 10.2, 2, 12a-H), 5.01 (1H, ddd, J = 17.07, 2.0, 1.7 Hz, 11b-H), 4.91-4.96 (2H, m, 11a & 12b-H), 2.59 (1H, dt, J = 9.5, 4.8 Hz, 2-H), 1.96-2.10 (1H, m, 14,17 & 9-H), 1.80-1.92 (1H, m, 15-H), 1.44-1.59 (2H, m, 3-H), 1.33-1.40 (2H, m, 8-H), 1.23-1.33 (6H, m, 5,6 & 7-H), 1.16-1.23 (2H, m, 4-H), 0.90 (3H, d, J =7.1 Hz, 16a/b-H), 0.80 (3H, d, J = 7.1 Hz, 16a/b-H)

^{13}C (125 MHz, $CDCl_3$) δ

212.78 (1-C), 139.11 (10-CH), 136.36 (13-CH), 117.54 (12-CH_2), 114.12 (11-CH_2), 55.29 (2-CH), 52.37 (14-CH), 33.73 (9-CH_2), 30.07 (17-CH_3), 29.82 (3-CH_2), 29.70 (5,6 or 7-CH_2), 29.24 (5,6 or 7-CH_2), 29.00 (5,6 or 7-CH_2), 28.85 (8-CH_2), 27.54 (4-CH_2), 27.26 (15-CH), 21.60 (16a/b-CH_3), 16.84 (16a/b-CH_3)

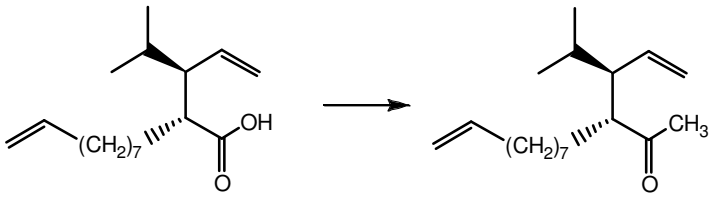
IR (thin film, ν_{max} cm^{-1}) 2926, 2855, 1731 C=O, 1639 C=O, 999, 910 vs C=C

Acc Mass (ESI):
Calc:$C_{18}H_{32}ONa$ 287.2345
Found: 287.2338 Error: 2.7 ppm
R_f 0.8 (dichloromethane)

<u>GC-MS</u>

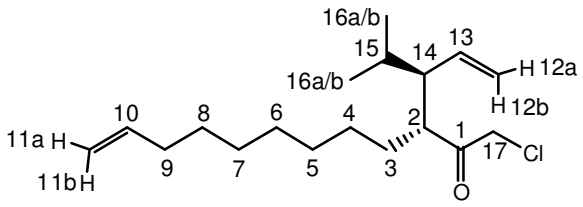
HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 10.46 minutes

Mass Spectrum (EI, Low resolution, integral with GC)
No molecular ion visible, 249 $(M\text{-}CH_3)^+$, 221 $(M\text{-}CH_3CO)^+$, 153, 140, 97,



To a solution of (*R**)-2-((*S**)-4-methylpent-1-en-3-yl)undec-10-enoic acid **363** (1.31 g, 0.0049 mol) in dry diethyl ether (30 ml) cooled to -30°C was added methyl lithium solution (1.6 M in diethyl ether, 6.25 ml, 0.01 mol) over 3 minutes. The solution was maintained at 0°C for 1 hr, then at ambient temperature for 2 hr, after which time the reaction appeared complete by TLC. The reaction was cooled to -5°C, and water (20 ml) was added, keeping the temperature below 0°C, then acidified to pH1 with a few drops of concentrated hydrochloric acid. The phases were separated, the aqueous phase extracted with further diethyl ether (3 x 30 ml), the combined organic phases washed with brine until neutral, dried over anhydrous sodium sulfate, and then passed over 20 minutes through a column of 5 ml Ambersep-900-OH (freshly regenerated, dehydrated with diethyl ether) to remove residual starting material. The solvent was then removed under reduced pressure, giving the title compound. 0.87 g, 67%.

(*R**)-1-chloro-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **422**
(novel)



Appearance: Colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.81 (1H, ddt, J = 17.0, 10.1, 6.7 Hz 10-H), 5.61 (1H, ddd, J = 10.1, 1.9 Hz, 13-H), 4.91-5.02 (3H, m, 11a,11b & 12b-H), 5.09 (1H, dd, J = 10.1, 1.9 Hz, 12a-H), 4.05 (1H, part of AB system J = 16.1 Hz, 17a-H), 4.07 (1H, part of AB system, J = 16.1 Hz, 17b-H), 2.86 (1H, dt, J = 9.4, 4.7 Hz, 2-H), 2.0-2.12 (3H, m, 14 & 9-H), 1.88 (1H, sept of d, J = 6.7, 2.2 Hz, 15-H), 1.51-1.61 (2H, m, 3-H), 1.1-1.4 (10H, m, 4,5,6,7 & 8-H), 0.89 (3H, d , J = 6.8 Hz, 16a/b-H), 0.82 (3H, d, J = 6.8 Hz)

^{13}C (125 MHz, $CDCl_3$) δ

205.38 (1-C), 139.08 (10-CH), 135.58 (13-CH), 118.59 (12-CH_2), 114.15 (11-CH_2), 52.60 (14-CH), 51.46 (2-CH), 50.14 (17-CH_2), 33.71 (9-CH_2), 29.96 (3-CH_2), 29.69 (4,5,6,7 or 8-CH_2), 29.18 (4,5,6,7 or 8-CH_2), 28.97 (4,5,6,7 or 8-CH_2), 28.83 (4,5,6,7 or 8-CH_2), 27.46 (4,5,6,7 & 8-CH_2), 27.29 (15-CH), 21.47 (16a/b-CH_3), 16.69 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 2926, 2855,1732 vs C=O, 1639 s C=O, 999, 910 vs C=C

Acc Mass (ESI):

Calc: $C_{18}H_{31}ClNaO$ 321.1956

Found: 321.1951 Error: 1.51 ppm

R_f 0.7 (1:1 petroleum ether:dichloromethane)

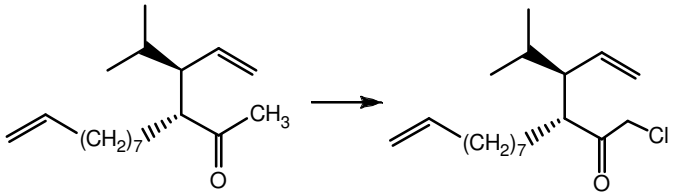
GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.49 minutes

Mass Spectrum (EI, Low resolution, integral with GC)

No molecular ion visible, 249 $(M\text{-}CH_2Cl)^+$, 221 $(M\text{-}ClCH_2CO)^+$,174, 131, 95, 83



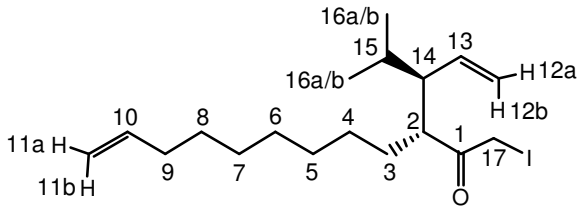
Method of Viseux,[48] with minor modifications.

Diisopropylamine* (0.357g, 0.5 ml, 0.00354 mol) was added to dry THF (10 ml) cooled to -10°, and methyl lithium (1.6 M in diethyl ether, 2 ml, 0.0032 mol) was added, maintaining the temperature below 0°. The solution was stirred for 10 minutes at 0°, then cooled to -78°. (*R**)-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **421** (0.528 g, 0.002 mol) previously dissolved in THF (5 ml) was added over 25 minutes, the solution warmed to 0°C for 30 minutes, then cooled to -78°C. A solution of *freshly recrystallized* N-chlorosuccinimide (0.42 g 0.00315 mol) in THF (10 ml) was added *fast* with vigorous stirring (exotherm to -55°C), stirred for 7 minutes (timed), and then saturated potassium carbonate solution (10 ml) added *fast*, maintaining fast stirring so as to produce a fine slurry . The reaction was warmed to 0°, stirred for 5 minutes, then the product extracted with diethyl ether (70 ml in 3 portions). The organic phases were washed with brine (20 ml x 2), then with brine containing a trace of sodium metabisulite (20 ml), and the ether phase tested for absence of N-chlorosuccinimide with starch/potassium iodide paper. The ethereal solution was then washed with brine (20 ml x 3) dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by chromatography using hexane/dichloromethane as eluent. The title compound was obtained 0.39 g 65%.

* purified by heating under reflux with calcium hydride for 20 minutes, then distilled from the calcium hydride and then stored in the dark over freshly activated 4Å molecular sieve, under nitrogen.

** Recrystallized immediately before use from benzene and dried *in vacuo* at ambient temperature. mp 149-150°C, lit 150-151° for 98% material.[200]

(*R**)-1-iodo-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **423**
(novel)



Appearance: pale brownish resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.81 (1H, ddt, J = 16.9, 10.2, 6.8 Hz 10-H), 5.60 (1H, ddd, J = 17.0, 10.2, 6.9 Hz, 13-H), 5.10 (1H, dd, J = 10.2, 2.0 Hz 12a-H), 4.94 (1H, dd, J =10.2, 1.9 Hz, 11a-H), 5.0 (1H, dd, J = 17.2, 1.8 Hz, 11b-H), 4.95 (1H, dd, J = 17.0, 2.0 Hz, 12b-H), 3.84 (1H, part of AB system, J = 11.7 Hz, 17a-H), 3.82 (1H, part of AB system, J = 11.7 Hz 17b-H), 2.96 (1H, dt, J = 9.3, 4.4 Hz, 2-H), 1.99-2.07 (3H, m, 9 & 14-H), 1.88 (1H, app oct, J ≈ 6.7 Hz, 15-H), 1.2-1.65 (12H, 3,4,5,6,7 & 8-H), 0.90 (3H, d, J = 6.7 Hz, 16a/b-H), 0.83 (3H, d, J = 6.7 Hz, 16a/b-H)

^{13}C (125 MHz, $CDCl_3$) δ

205.36 (1-C), 139.12 (10-CH), 135.95 (13-CH), 118.45 (12-CH_2), 114.13 (11-CH_2), 53.00 (14-CH), 52.69 (2-CH), 33.73 (9-C), 30.04 (3,4,5,6,7 or 8-CH_2), 29.68 (3,4,5,6,7 or 8-CH_2), 29.20 (3,4,5,6,7 or 8-CH_2), 29.00 (3,4,5,6,7 or 8-CH_2), 28.84 (3,4,5,6,7 or 8-CH_2), 27.64 (3,4,5,6,7 or 8-CH_2), 27.40 (15-CH), 21.60 (16a/b-CH_3), 16.95 (16a/b-CH_3), 10.02 (17-CH_2)

IR (thin film, ν_{max} cm^{-1}) 2925, 2855, 1705 (vs) C=O,1639 C=O, 1463, 998 C=C, 910 C=C vs

Acc Mass (ESI):

Calc: $C_{18}H_{31}IONa$ 413.1312

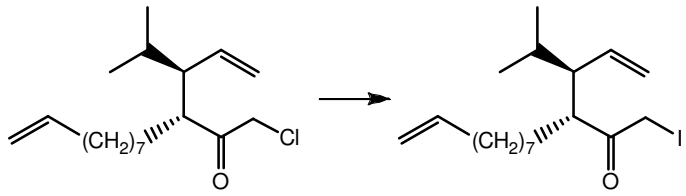
Found: 413.1309 Error: 0.58

R_f 0.9 (1:1 dichloromethane: petroleum ether)

GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.73 minutes

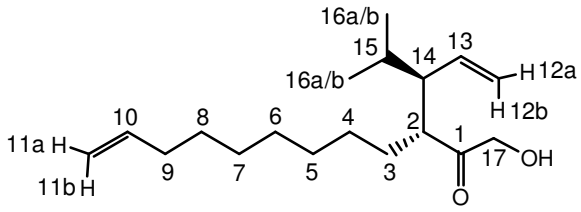
Mass Spectrum (EI, Low resolution, integral with GC)
347 $(M-C_3H_7)^+$, 263 $(M-I)^+$, 223, 169, 95, 83, 55



Method of Pace and co-workers,[149] generic Finkelstein iodination.

To a solution of (*R**)-1-chloro-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **422** (0.22 g, 0.000736 mol) in acetone (7 ml), was added sodium iodide (0.4 g, 0.00267 mol) and the whole stirred briskly under nitrogen for 17 hrs. GC indicated reaction to be essentially complete. The reaction was diluted with diethyl ether (40 ml), washed with brine (5 x 10 ml), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give the title compound 0.251 g, 87%.

(*R**)-1-hydroxy-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **425**
(novel)



Appearance: colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.81 (1H, ddt, J = 16.9, 10.2, 7.0 Hz, 10-H), 5.55 (1H, ddd, J = 17.0, 10.2, 7.0 Hz, 13-H), 5.07 (1H, J = 10.5, 2.2 Hz, 12a-H), 5.0 (1H, dd, J = 17.0, 2.2 Hz, 11b-H), 4.90-4.96 (2H, m, 11a & 12b-H), 4.17 (2H, d, J = 4.5 Hz, 17-H), 3.14 (1H, t, J = 4.5 Hz, O**H**), 2.60 (1H, app dt, J = 9.2, 5.3, 2-H), 2.0-2.12 (3H, m, 14 & 9-H), 1.80-1.90 (1H, m, 15-H), 1.5-1.6 (3H, m, 3-H), 1.31-1.42 (2H, m, 8-H), 1.13-1.31 (8H, m, 4,5,6,7 & 8-H), 0.89 (3H, d, J = 6.7 Hz, 16a/b-H), 0.81 (3H, d, J = 6.7 Hz, 16a/b-C)

^{13}C (125 MHz, $CDCl_3$) δ

213.44 (1-C), 139.07 (10-CH), 135.53 (13-CH), 118.40 (12-CH_2), 114.16 (11-CH_2), 70.01 (17-CH_2), 52.33 (14-CH), 50.25 (2-CH), 33.70 (9-CH_2), 29.99 (3,4,5,6,7 or 8-CH_2), 29.67 (3,4,5,6,7 or 8-CH_2), 29.18 (4,5,6,7 or 8-CH_2), 28.97 (4,5,6,7 or 8-CH_2), 28.82 (4,5,6,7 or 8-CH_2), 27.42 (4,5,6,7 or 8-CH_2), 27.36 (15-CH), 21.45 (16a/b-CH_3), 16.83 (16a/b-CH_3)

IR (thin film, ν_{max} cm^{-1}) 3481 (OH, vs), 2925 (vs), 2854 (vs), 1715 (C=O vs),1640, 1464, 1370, 1266, 1037, 998

Acc Mass (ESI):

Calc: $C_{18}H_{32}O_2Na$ 303.2295

Found: 303.2270 Error: 8.06 ppm

R_f 0.6 (1:1 petroleum ether:dichloromethane)

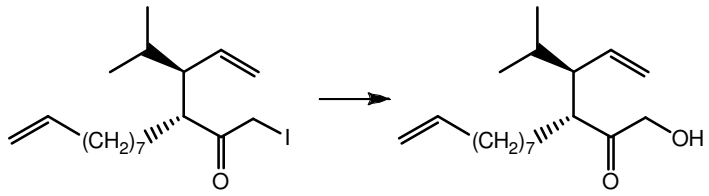
GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min

Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.02 minutes

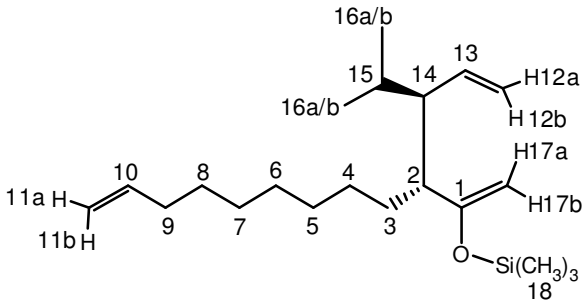
Mass Spectrum (EI, Low resolution, integral with GC)

249 (M-(CH_2-OH))$^+$, 231, 175,123, 109, 95, 83, 69, 55



(*R**)-1-iodo-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **423** (19.5 mg, 0.00005 mol) was dissolved in dimethylformamide (1 ml, anhydrous, as supplied), and added to sodium nitrite (6 mg, 0.000075 mol) and phloroglucinol (10 mg 0.00007 mol) in a sealed vial, which was purged with nitrogen and stirred overnight at ambient temperature . GC showed complete reaction. The reaction was diluted with diethyl ether (20 ml), washed with brine (10 ml x 6), dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by chromatography (using dichloro-methane:petroleum ether as eluent) to give the title compound, 2 mg 13%.

Trimethyl((*R**)-3-((S*)-4-methylpent-1-en-3-yl)dodeca-1,11-dien-2-yloxy)silane **447** (novel)



Appearance: Colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.82 (1H, ddt, J = 16.9, 10.2, 6.7 Hz, 10-H), 5.61 (1H, app dt, J = 17.1, 10.0 Hz, 13-H), 5.0 (1H, dd, J =17.1, 1.7 Hz, 11b-H), 4.92-4.97 (2H, m, 12a & 11a-H), 4.83 (1H, dd, J = 17.1, 2.5 Hz, 12b-H), 3.95 (1H, s, 17b-H*), 3.90 (1H, s, 17a-H*), 2.0-2.10 (1H, m, 9 & 2-H), 1.7-1.82 (2H, m, 14 & 15-H), 1.1-1.44 (14H, m, 3,4,5,6,7 & 8-H), 0.91 (3H, d, J = 6.7 Hz, 16a/b-H), 0.78 (3H, d, J =6.7, 16a/b-H), 0.2 (9H, s, 18-H)

* 17a and 17b differentiated by NOE, see page 202

^{13}C (125 MHz, $CDCl_3$) δ

159.69 (1-C), 139.24 (10-CH), 138.84 (13-CH), 115.18 (12-CH_2), 114.03 (11-CH_2), 89.82 (17-CH_2), 53.65 (14-CH**), 47.21 (2-CH), 33.81 (9-CH_2), 30.36 (3,4,5,6,7 or 8-CH_2), 29.64 (3,4,5,6,7 or 8-CH_2), 29.46 (3,4,5,6,7 or 8-CH_2), 29.11 (3,4,5,6,7 or 8-CH_2), 29.11 (3,4,5,6,7 or 8-CH_2), 28.93 (3,4,5,6,7 or 8-CH_2), 27.76 (15-CH**), 27.38 (3,4,5,6,7 or 8-CH_2), 21.85 (16a/b-CH_3), 18.69 (16a/b-CH_3), 0.07 (18-CH_2)

**14 & 15 differentiated by H2BC

IR (thin film, ν_{max} cm^{-1}) ,2931,2854,1644,1617,1466

Acc Mass (ESI): Unstable to ESI conditions, ketone **421** obtained

Low resolution (EI) 336 M^+, 321 $(M\text{-}CH_3)^+$, 293, 279, 254, 225

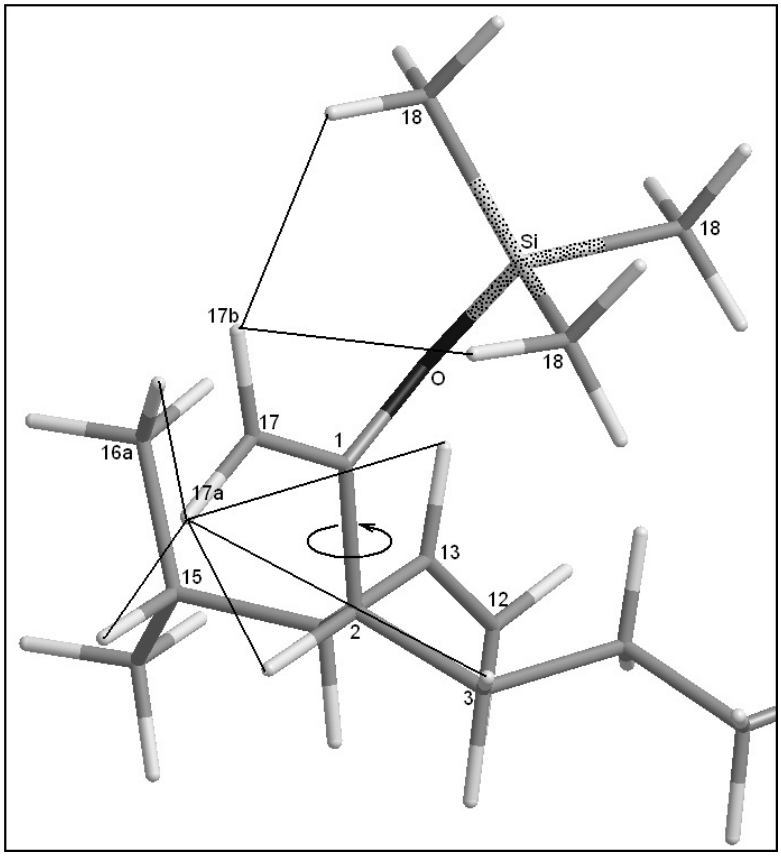
Rf 0.6 (1:1 dichloromethane:petroleum ether)

GC-MS

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 10.56 minutes

Mass Spectrum (EI, Low resolution, integral with GC)
336 M^+, 321 $(M\text{-}CH_3)^+$, 293, 239, 225

NOESY (NOE) Identification of Hydrogens 17a and 17b in **447**

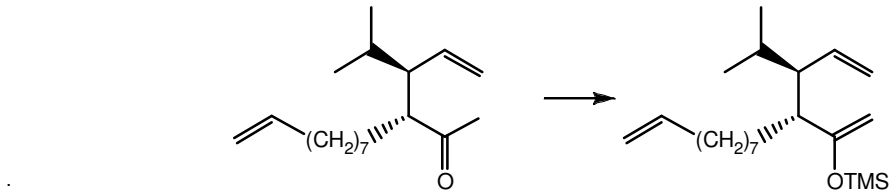


The above conformation has been energy-minimized.[100] It will be seen that rotation of the CH_2=C-O-TMS group about the bond C1-C2 brings the hydrogen atom 17a-H close to 16a-H, 15-H, 2-H, 3-H, and 13-H. The hydrogen 17b-H is *always* further away from *any* of these than 17a-H. By contrast, 17b-H is *always* closer to one or more of the hydrogens (18-H) on the TMS methyl groups than 17a-H. These are consistent with the observed correlations, shown in the table below.

	16a-H	15-H	2-H	3-H	13-H	18-H
17a-H δ = 3.90	✓	✓	✓	✓	✓	✗
17b-H δ = 3.95	✗	✗	✗	✗	✗	✓

(✓ = Correlation observed, ✗ = No correlation observed)

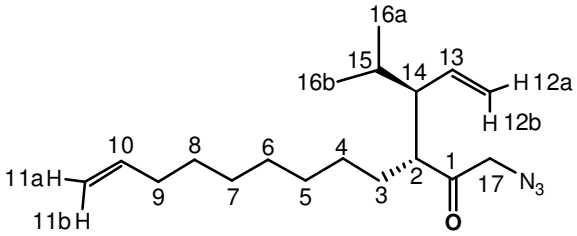
On the basis of the above, the signal at δ = 3.95 is 17b-H, that at δ = 3.90 is 17a-H.



Method patterned on that of Campbell and co-workers.[163]

(*R**)-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **421** (20 mg, 0.000076 mol), was dissolved in dry acetonitrile (2 ml) and placed in a vial, with a stirrer bar and potassium iodide (20mg 0.00012 mol). To this were added TMSCl (2 drops) and dry triethylamine (4 drops) and the whole warmed to 50°C for 1 hr, after which time the reaction appeared complete by GC. Heating was discontinued, and the solvents removed in a slow stream of nitrogen. The residue was dissolved in dry dichloromethane, and purified by chromatography using neat dichloromethane as eluent. The solvent was then removed under reduced pressure. 17mg, 66%

(*R**)-1-azido-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **280**
(novel)



.

Appearance: colourless resin

^{1}H NMR (500 MHz, $CDCl_3$) δ

5.81 (1H, ddt, J = 17.0, 10.2, 6.6 Hz 10-H), 5.59 (1H, app t, J = 17.0, 10.2 Hz 13-H), 5.11 (1H, dd, J = 10.2, 1.5 Hz 12a-H), 5.0 (1H, dd, J = 17.0, 1.6 Hz, 11b-H), 4.96 (1H, d, J = 17.0 Hz, 12b-H), 4.94 (1H, d, J = 10.0 Hz, 11a-H), 3.88 (1H, part of AB system, J = 18.2 Hz 17a-H), 3.80 (1H, part of AB system, J = 18.2 Hz, 17b-H), 2.63 (1H, td, J = 9.2, 5.7 Hz, 2-H), 2.0-2.12 (3H, m, 14 & 9-H), 1.82-1.94 (1H, m, 15-H), 1.51-1.54 (2H, m, 3-H), 1.1-1.4 (10H, m, 4,5,6,7 & 8-H), 0.89 (3H, d, J = 6.8 Hz 16a/b-H), 0.82 (3H, d, J = 6.86 Hz 16a/b-H)

^{3}C (125 MHz, $CDCl_3$) δ

208.00 (1-C), 139.07 (10-CH), 135.53 (13-CH), 118.75 (12-CH_2), 114.17 (11-CH_2), 58.93 (17-CH_2), 52.42 (14-CH), 51.47 (2-CH), 33.71 (9-CH_2), 29.81 (3-CH_2), 29.69 (4,5,6,7 or 8-CH_2), 29.18 (4,5,6,7 or 8-CH_2), 28.97 (4,5,6,7 or 8-CH_2), 28.82 (4,5,6,7 or 8-CH_2), 27.54 (4,5,6,7 or 8-CH_2), 27.23 (15-CH), 31.44 (16a/b-CH_3), 16.56 (16a/b-CH_3)

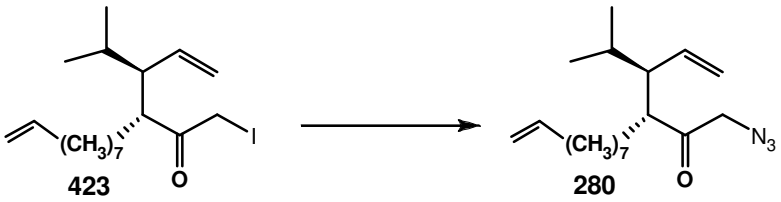
IR (thin film, ν_{max} cm^{-1}) 2926, 2855, 2101 (vs, azide), 1723 (C=O), 1639, 1464, 1279

Acc Mass (ESI):
Calc: $C_{18}H_{31}N_3NaO$ 328.2359
Found: 328.2357 Error: 0.71 ppm
R_f 0.5 (1:1 40/60 petroleum ether:dichloromethane)

<u>GC-MS</u>

HP5M5 Column, 30m long, 1/4mm ID, ¼ micron film, flow rate 1.3 ml/min
Thermal cycle 50°C isothermal for 4 minutes, ramped at 30°C per minute to 300°C, then 4 minutes isothermal. Retention time 11.33 minutes

Mass Spectrum (EI, Low resolution, integral with GC) 263, 204, 236, 166



423 **280**

(*R**)-1-iodo-3-((*S**)-4-methylpent-1-en-3-yl)dodec-11-en-2-one **423,** (103 mg, 0.000264 mol) was dissolved in dry, distilled acetone (5 ml) and stirred at ambient temperature with sodium azide (51.5 mg, 0.000792 mol) for 5 days, after which time GC indicated no starting material remained. The solvent was evaporated in a stream of dry nitrogen and the residue subjected directly to chromatography with dichloromethane/hexane.
28 mg 34%

Chapter 4 References

1) Hayakawa, Y.; Kawakami K.; Seto H.; Furihata K. *Tetrahedron Lett.* **1992**, *33* (19), 2701-2704.

2) Boger D.L.; Hong J. *J. Am. Chem. Soc.* **2001,** *123* (35), 8515-8519.

3) Fürstner A.; Reinecke K.; Prinz H.; Waldman H. *ChemBioChem* **2004,** *5,* 1575-1579.

4) Fürstner A. *Angew. Chem., Int. Ed.* **2003,** *42* (31), 3582-3603.

5) *Streptomyces griseoviridis* Strain K61 (129069) Fact Sheet; US Environmental Protection Agency: Washington DC, May 2000 http://www.epa.gov/opp00001/biopesticides/ingredients/factsheets/factsheet_129069.htm (Accessed 9/8/12).

6) *Streptomyces K61* (formerly *Streptomyces griseoviridis*) SANCO/1865/08; Review report for the active substance for the European Commission Health and Consumers Directorate-General: June 2008 http://ec.europa.eu/food/plant/protection/evaluation/existactive/K61.pdf (Accessed 9/8/12).

7) Fűrstner A.; Weintritt H. *J. Am. Chem. Soc.* **1997**, *119* (12), 2944-2945.

8) Fűrstner A.; Weintritt H. *J. Am. Chem. Soc.* **1998,** *120* (12), 2817-2825.

9) Astruc D. *New J. Chem.* **2005**, 29 (1), 42–56.

10) Kim S.H.; Figuera I.; Fuchs P.L. *Tetrahedron Lett.* **1997**, *38* (15), 2601-2604.

11) Bamford S.J.; Luker T.; Speckamp N.; Hiemstra H. *Org. Lett.* **2000**, *2*(8),1157-1159.

12) Salamone S.G.; Dudley G.B. *Org. Lett.* **2005,** *7* (20), 4443-4445.

13) Fűrstner A.; Gastner T.; Weintritt H. *J. Org. Chem.* **1999,** *64* (7), 2361-2366.

14) Kim S.H.; Fuchs P.L. *Tetrahedron Lett.* **1996**, 37 (15), 2545-2548.

15) Barton D.H.R; McCombie S.W. *J. Chem. Soc., Perkin Transactions 1* **1975,** (16), 1574-1585.

16) Bitar A.J.; Frontier A.J. *Org. Lett.* **2009**, 11 (1), 49-52.

17) Takashi M.; Itoh I.; Shibata N.; Nakatani S.; Kato T.; Terashima S. *Tetrahedron Lett.* **1998**, 39 (39), 6911-6914.

18) Nakatani S.; Kirihara M.; Yamada K.;Terashima S. *Tetrahedron Lett.* **1995**, *36* (46), 8461-8464.

19) Krapcho A.P. *ARKIVOC,* **2007**, (ii) 1-53.

20) Fagan M.A.; Knight D.W. *Tetrahedron Lett.* **1999,** *40* (33), 6117-6120.

21) Song C.; Knight D.W.; Whatton M.A. *Org. Lett.* **2006,** *8* (1), 163-166.

22) Song C.; Knight D.W.; Whatton M.A. *Tetrahedron Lett.* **2004**, *45* (51), 9573-9576.

23) Denmark, S.E. The Nazarov and Related Cationic Cyclizations. In *Comprehensive Organic Synthesis;* Paquette, L.A., Ed.; Pergamon Press: Oxford, 1991; Vol 5**,** pp 751–784.

24) Song C.; Liu H.; Hong M.; Liu Y.; Jia F.; Sun I.; Pan Z.; Chang J. *J. Org. Chem.* **2012**, *77* (1), 704-706.

25) Harrington P.E.; Tius M.A. *Org. Lett.* **1999,** *1*(4)*,* 649-651.

26) Stetter H.; Schreckenberg M. *Angew. Chem., Int. Ed.* **1973,** *12* (1)*,* 81.

27) Harrington P.E.; Tius M.A. *Org. Lett.* **2000**, *2* (16), 2447-2450.

28) Harrington P.E.; Tius M.A. *J. Am. Chem. Soc.* **2001**, 1*23* (35), 8509-8514.

29) Robertson J.; Hatley R.J.D. *Chem. Commun. (Cambridge, U.K.)* **1999,** (16) 1455-1456.

30) Robertson J.; Hatley R.J.D. *J. Chem. Soc., Perkin Trans. 1* **2000,** (20) 3389-3396.

31) Finkelstein H. *Ber. Dtsch. Chem. Ges*. **1910,** *43* (2), 1*528-1532.*

32) Trost B.M.; Doherty G.A. *J. Am. Chem. Soc.* **2000,** 1*22* (16), 3801-3810.

33) *Organic Syntheses*; Wiley & Sons: New York, 1988; VI p 368-372.

34) Corey E.J.; Yu C.M.; Lee D.H *J. Am. Chem. Soc.* **1990,** 1*12* (2), 878-879.

35) Luker T.; Koot W.J.; Hiemstra H. *J. Org. Chem.* **1998,** *63* (2), 220-221.

36) Koot W.J.; Hiemstra H.; Speckamp W.N. *J. Org. Chem.* **1992,** *57* (4), 1059-1061.

37) Boger D.L. *Chem. Rev.* **1986,** *86* (5), 781-793.

38) Dyke C.A.; Bryson T.A. *Tetrahedron Lett.* **2004,** *45* (31), 6051-6053.

39) Bosch I.; Romea P.; Urpi F.; Vilarrasa J. *Tetrahedron Lett.* **1993,** *34* (29), 4671-4674.

40) Occhiato E.G.; Prandi C.; Ferrali A.; *J. Org. Chem.* **2005,** *70* (11), 4542-4545.

41) Stille J.K. *Angew. Chem., Int. Ed.* **1986**, *25* (6), 508-524.

42) Farina V.; Krishan B. *J. Am. Chem. Soc.* **1991,** *113* (25), 9585-9595.

43) Buono F.; Tenaglia A. *J. Org. Chem.* **2000,** *65* (12), 3869-3874.

44) Malona J.A.; Colbourne J.M.; Frontier A.J. *Org. Lett.* **2006**, *8* (24) 5661-5664.

45) Nicolaou K.C.; Bulger P.G.; Sarlah D. *Angew. Chem., Int. Ed.* **2005**, 44 (29), 4442-4489.

46) Kerr D.J.; Flynn B.L. *Org. Lett.* **2012,** *14* (7), 1740-1743.

47) Kerr D.J.; White J.M.; Flynn B.L. *J. Org. Chem.* **2010,** *75* (21), 7073-7084.

48) Viseux E.M.E. Synthetic Studies Towards a Total Synthesis of Roseophilin. D. Phil. Thesis, University of Sussex, January 2005.

49) Bouglas R.A. Studies Towards the Total Synthesis of Roseophilin. D. Phil. Thesis, University of Sussex, May 2008.

50) McFarland C.M.; McIntosh M.C. The Ireland-Claisen Rearrangement (1972-2004). In *The Claisen Rearrangement*; Hiersemann M.; Nubbermeyer U., Eds.; Wiley-VCH Verlag GmbH &Co KgaA: Weinheim, 2007 pp 117-205.

51) Staudinger H.; Meyer J. *Helv. Chim. Acta.* **1919**, *2*, 635-646.

52) Palacios F.; Concepcion A.; Aparicio D.; Rubiales G.; de los Santos J.M. *Tetrahedron* **2007**, *63* (3), 523–575.

53) Viseux E.M.E.; Parsons P.J.; Pavey J.B.J.; Carter C.M.; Pinto I. *Synlett* **2003,** (12), 1856-1858.

54) Moody C.J.; Doyle K.J. The Synthesis of Oxazoles from Diazocarbonyl Compounds. In *Progress in Heterocyclic Chemistry Vol 9*; Gribble G.W.; Gilchrist T.L., Eds.; Pergamon, Oxford, 2007, pp 1-16.

55) Gabriel S. *Ber. Dtsch. Chem. Ges*. **1887,** *20* (2), 2224-2236.

56) Ragnarsson U.; Grehn l. *Acc. Chem. Res.* **1991,** *24* (10), 285–289.

57) Ono N. *The Nitro Group in Organic Synthesis;* John Wiley & Sons: New York, 2001; pp 30-69.

58) a) Wittig G.;Schöllkopf U. *Chem. Ber.* **1954,** *87* (9), 1318-1330.
b) Wittig G.; Haag W. *Chem. Ber.* **1955,** 88 (11), 1654-1666.

59) Vedejs E.; Marth C.F. *J. Am. Chem. Soc.* **1990,** *112* (10), 3905-3909.

60) Berger S.; Neumann R.A. *Eur. J. Org. Chem.* **1998,** (6) 1085-1087.

61) Horner L.; Hoffmann H.; Wippel H.G.; Klahre G. *Chem. Ber.* **1959,** 92 (10), 2499-2505.

62) Clayden J.; and Warren S. *Angew. Chem., Int. Ed.* **1996,** *35* (3), 241-270.

63) Wadsworth W.S.; Emmons W.D. *J. Am. Chem. Soc.* **1961,** *83* (7), 1733-1738.

64) Boutagy J.; Thomas R. *Chem. Rev.* **1974,** 74 (1) 87-99.

65) Kürti L.; Czakó B. *Strategic Applications of Named Reactions in Organic Synthesis;* Elsevier Academic Press: London, 2005; pp 212-215.

66) Lefebre G.; Seyden-Penne J. *J. Chem. Soc. D* **1970,** (20), 1308-1309.

67) Thompson S.K.; Heathcock C.H. *J. Org. Chem.* **1990**, *55* (10), 3386-3388.

68) Nagaoka H.; Kishi N. *Tetrahedron* **1981,** 37 (23), 3873-3888.

69) Jones G.; Maisey R.F. *Chem. Commun. (London)* **1968,** (24) 543-545.

70) Kinstle T.H.; Mandanas B.Y. *Chem. Commun. (London)* **1968,** (24), 1699-1700.

71) Ando K. *J. Org. Chem.* **1999,** *64* (18), 6815-6821.

72) Ando K. *J. Org. Chem.* **1997**, *62* (7), 1934-1939.

73) Still W.C.; Gennari C. *Tetrahedron Lett.* **1983***, 24* (41), 4405-4408.

74) Bhattacharya A.K.; Thyagarajan G. *Chem. Rev.* **1981**, *81* (4), *415-430.*

75) Viseux E.M.E., personal communication.

76) Unpublished industrial work by the author.

77) Petroski R.J.; Weisleder D. *Synth. Commun.* **2001**, *31* (1), 85-89.

78) Claridge D.W.; Davies S.G.; Lee J.A.; Nicholson R.L.; Roberts P.M.; Russell A.J.; Smith A.D.; *Org. Lett.* **2008,** *10* (23), 5437-5440.

79) Murray A.J. personal communication

80) T*he Organic Chemist's Companion* (Merlic group website, UCLA) http://www.chem.ucla.edu/research/org/MERLIC_GROUP/Lab_Notes.html#Workup_Aluminum (Accessed 12/7/12) The same procedure appears on the Frontier group website (Rochester), credited to the Merlic group website (URL above) and also at various other locations on the internet. Its original source is unknown.

81) Fieser L.F.; Fieser M. *Reagents for Organic Synthesis;* John Wiley & Sons: New York, 1967, p 584.

82) Rao A.V.R.; Mysorekar S.V.; Yadav J.S. *Synth. Commun.* **1987,** *17* (11), 1339-1347.

83) Amberlyst® A26-OH Product Data Sheet 0322A;Rohm & Haas:Philadelphia PA, April 2001. http://www.dow.com/product-line/amberlyst/product/amberlyst-a26-oh/ (Accessed 4/12/11; widely downloadable from other suppliers of this resin.)

84) Pierce A.E. *Silylation of Organic Compounds: A Technique for Gas-Phase Analysis;* Pierce Chemical Co.: Illinois,1968.

85) Van Look, G.; Simchen, G.; Heberle J. *Silylating agents : derivatization reagents, protecting-group reagents, organosilicon compounds, analytical applications, synthetic applications*; Fluka Chemie AG: Buchs,1995. Downloadable from Aldrich website:- http://www.sigmaaldrich.com/etc/medialib/docs/Aldrich/General_Information/silylation_overview.Par.0001.File.tmp/silylation_overview.pdf (Accessed 15/7/12).

86) Aldrich/Supelco Catalogue No 33148.

87) Ireland R.E.; Mueller R.H. *J. Am. Chem. Soc.* **1972,** *94* (16), 5897-98.

88) Corey E.J.; Gross A.W.; *Tetrahedron Lett.* **1984,** *25* (5), 495-498.

89) Heathcock C.H.; Buse C.T.; Kleschick W.A., Pirrung M.C.; Sohn J.E.; Lampe J. *J. Org. Chem.* **1980,** *45* (6), 1066-1081.

90) Ireland R.E.; Wipf P.; Armstrong J.D. *J. Org. Chem.* **1991,** *56* (2), 650-657.

91) Parsons P.J., Viseux E.M., Pennicott L.E., Bouglas R.A. personal communications.

92) *The Merck Index (9th Edition)*; Merck & Co: Rathway,1976, monograph 9505, p 1264.

93) Ereaux L.P.; Craig G.E. *Can. Med. Assoc. J.* **1949,** *61* (4), 361-364.

94) Leydet A.; El Hachemi H.; Boyer B.; Lamaty G.; Roque J.P.; Schols D.; Snoeck R.; G. Andrei G.; Ikeda S.; Neyts J.; Reymen D.; J. Este J.; Witvrouw M.; De Clercq E. *J. Med. Chem.* **1996,** *39* (8), 1626-1634

95) Ambersep® 900-OH Product Data Sheet 0480; Rohm & Haas:Philadelphia PA, March 2000. http://www.lenntech.com/Data-sheets/Ambersep-900-OH-L.pdf (Accessed 4/12/11; widely downloadable from other suppliers of this resin.)

96) Parsons P.J.; Pennicott L.; Eshelby J.; Goessman M.; Highton A.; Hitchcock P. *J. Org. Chem.* **2007,** *72* (24), 9387-9390.

97) Koch G.; Janser P.; Kottirsch G.; Romero-Giron E. *Tetrahedron Lett.* **2002,** *43* (27), 4837–4840.

98) Fieser L.F.; Fieser M. *Reagents for Organic Synthesis Vol 6;* John Wiley & Sons: New York, 1977 p 134.

99) *MestReNova,* version 6.0.2-5475; Mestrelab Research SL: Santiago de Compostela, Spain.

100) *Chem3D Ultra,* version 10.0; CambridgeSoft:Cambridge MA (MM2 calculation used)

101) Amberlyst® A21 Product Data Sheet 0324A; Rohm & Haas:Philadelphia PA, Sept 01.
http://www.dow.com/assets/attachments/business/process_chemicals/amberlyst/amberlyst_a21/tds/amberlyst_a21.pdf
(Accessed 4/12/11; widely downloadable from other suppliers of this resin.)

102) Amberlite™ IRA-67 Product Data Sheet 0226A; Rohm & Haas:Philadelphia PA, January 2008.
http://www.dow.com/assets/attachments/business/ier/ier_for_industrial_water_treatment/amberlite_ira67/tds/amberlite_ira67.pdf
(Accessed 4/12/11; widely downloadable from other suppliers of this resin.)

103) Metz P.; Hungerhoff B.; *J. Org. Chem.* **1997,** *62* (13), 4442-4448.

104) Levene P.A.; Taylor F.A. *J. Biol. Chem.* **1918,** *35* (2), 281-283.

105) House H.O.; Haack J.L.; McDaniel W.C.; VanDerveer D. *J. Org. Chem.* **1983,** *48* (10), 1643-1654.

106) Schröder M. *Chem. Rev.* **1980,** *80* (2), 187-213.

107) Hoffman K.A. *Ber. Dtsch. Chem. Ges*. **1912,** *45* (3), 3329-3336.

108) Hofmann K.A.; Ehrhart O.; Schneider O. *Ber. Dtsch. Chem. Ges.* **1913,** *46* (2),1657-1668.

109) Milas N.A.; Sussman S. *J. Am. Chem. Soc*. **1936,** *58* (7), 1302-1304.

110) Milas N.A.; Sussman S. *J. Am. Chem. Soc.* **1937,** *59* (11), 2345-2347.

111) Criegee R. *Justus Liebigs Ann. Chem.* **1936,** *522* (1), 75-96.

112) Criegee R.; Marchand B.; Wannowius H. **1942,** *Justus Liebigs Ann. Chem. 550* (1)*,* 99-133

113) Collin R.J.; Jones J.; Griffith W.P. *J. Chem. Soc., Dalton Trans.* **1974,** (10), 1094-1097.

114) Corey E.J; Noe M.C.; Grogan M.J *Tetrahedron Lett.* **1996,** *37* (28), 4899-4902.

115) Sharpless K.B.; Teranishi A.Y.; Backvall J.E. *J. Am. Chem. Soc.* **1977,** *99* (9), 3120-3128.

116) Seiple I.B. *Controversial Mechanisms in Organic Synthesis*;
Baran Group Meeting, Scripps Research Institute 18/9/2010
http://www.scripps.edu/baran/images/grpmtgpdf/Seiple_Sept_10.pdf
(Accessed 21/7/2012).

117) Del Monte A.J.; Jan Haller J.; Houk K.N.; Sharpless K.B.; Singleton D.A.; Strassner T.; Thomas A.A. *J. Am. Chem. Soc.* **1997,** *119* (41), 9907-9908.

118) Sharpless K.B.; Akashi K. *J. Am. Chem. Soc.* **1976,** *98* (7), 1986-1987.

119) Van Rheenen V.; Kelly R.C.; Cha D.Y. *Tetrahedron Lett.* **1976,** *17* (23), 1973-1976.

120) Pappo R.; Allen D.S.; Lemieux R.U.; Johnson W.S. *J. Org. Chem.* **1956,** *21* (4), 478-479.

121) Buist G.J.; Bunton C.A. *J. Chem. Soc.* **1954,** 1406-1413.

122) Rylander P.N.; Steele D.R. *Tetrahedron Lett.* **1969,** *10* (20), 1579-1583.

123) Zhdankin V.V.; Stang P.J. *Chem. Rev.* **2008,** *108* (12), 5299-5358.

124) Dess D.B.; Martin J.C. *J. Am. Chem. Soc.* **1991,** *113* (19), 7277-7287.

125) Ohfune Y.; Hori K. *Tetrahedron Lett.* **1986,** *27* (50), 6079-6082.

126) Hanessian S.; Claridge S.; Johnstone S. *J. Org. Chem.* **2002,** *67* (12), 4261-4274.

127) Yang J.W.; Han H.; Roh E.J.; Lee S.; Song C.E. *Org. Lett.* **2002,** *4* (26), 4685-4688.

128) Amberlite XAD-4 Product Data Sheet 0556A; Rohm & Haas:Philadelphia PA, October 2003 http://www.dow.com/assets/attachments/business/process_chemicals /amberlite_xad/amberlite_xad4/tds/amberlite_xad4.pdf (Accessed 2/06/12; widely downloadable from other suppliers of this resin).

129) Hubbard K.I.; Finch J.A.; Darling G.D. *React. Funct. Polym.* **1998,** *36* (1),1-16.

130) Criegee R. *Angew. Chem., Int. Ed.* **1975,** *14* (11), 745-752.

131) Henne A.L.; Hill P. *J. Am. Chem. Soc.* **1943,** *65* (5), 752-754.

132) Bunnelle W.H *Chem. Rev.* **1991,** *91* (3), 335-362.

133) Church J.M.; Whitmore F.C.; McGrew R.V. *J. Am. Chem. Soc.* **1934,** *56*(1),176-184 and references therein.

134) Greenwood F.L. *J. Org. Chem.* **1955***, 20* (6), 803-807.

135) Knowles W.; Thompson Q. *J. Org. Chem.* **1960,** *25* (6), 1031-1033.

136) De Vries J.G.; Kellogg R.M. *J. Org. Chem.* **1980,** *45* (6), 4126-4129.

137) Jiménez T.; Barea E.; Oltra J.E.; Cuerva J.M.; Justicia J. *J. Org. Chem.* **2010,** *75* (20), 7022–7025.

138) Flippin L.A.; Gallagher D.W.; Jalali-Araghi K. *J. Org. Chem.* **1989,** *54* (6), 1430-1432.

139) Ranu B.C. *Synlett* **1993,** (12), 885-892.

140) Ranu B.C.; Chakraborty R. *Tetrahedron Lett.* **1990,** *31* (52), 7663-7664.

141) *CRC Handbook of Chemistry and Physics 60th Edition*; Weast R.C.; Astle M.J. Eds.; CRC Press: Boca Raton FA, p D125.

142) Browder C.C. *Curr. Org. Synth.* **2011,** *8* (5), 628-644.

143) Namboothiri I.N.N.; Rastogi R. Isoxazolines from Nitro Compounds: Synthesis and Applications. In *Topics in Heterocyclic Chemistry Vol 12*; Hassner A. Ed.; Springer-Verlag: Berlin, Heidelberg, 2008 pp 1-44 and refs therein.

144) Jäger V.; Buss V.; Schwab W. *Tetrahedron Lett.* **1978,** *19* (34), 3133-3136.

145) Baraldi P.G.; Barco A.; Benetti S.; Ferretti V.; Pollini G.P.; Polo E.; Zaniratoet V. *Tetrahedron* **1989,** *45* (5), 1517-1532.

146) Kinzel O.; Llauger-Bufi L.; Pescatore G.; Rowley M.;Schultz-Fademrecht C.; Monteagudo E.; Fonsi M.; Gonzalez Paz O.; Fiore F.; Steinkuhler C.; Jones P. *J. Med. Chem.* **2009,** *52* (11), 3453-3456.

147) Clibbens D.A.; Nierenstein M. *J. Chem. Soc., Trans.* **1915,** *107,* 1491-1494.

148) Jorgenson, M.J. Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. In *Organic Reactions, Vol. 18;* Dauben W.G. Ed.; John Wiley and Sons, Inc.: New York, 1970, p 1-98.

149) Pace V.; Martínez F.; Nova C.I.; Fernández M.; Sinisterra J.V.; Alcántara A.R. *Tetrahedron Lett.* **2009***, 50* (25), 3050-3053.

150) Commercially available *e.g.* Aldrich Catalogue 72580-10g.

151) Gelbard G.; Colonna S. *Synthesis* **1977,** (2), 113-116.

152) Jiminez Barrera R.M. Studies Towards the Total Synthesis of Asteriscanolide D.Phil. Thesis, University of Sussex, April 2011.

153) Meyer V.; Stüber O. *Ber. Dtsch. Chem. Ges*. ***1872,*** (1) 203-205; ***1872,*** *5* (1) 399-406; ***1872,*** *5* (1) 514-518.

154) Hammond G.S.; Hawthorne M.F.; Waters J.H.; Graybill B.M. *J. Am. Chem. Soc.* **1960,** 82 (3), 704-711.

155) Agrawal J.P.; Hodgson R.D. *Organic Chemistry of Explosives*; John Wiley and Sons: Chichester, 2007, p 8-11.

156) Lucas A. *Ber. Dtsch. Chem. Ges*. **1899,** 32 (3), 3179-3182.

157) Kornblum N.; Blackwood R.K.; Powers J.W. *J. Am. Chem. Soc.* **1957,** *79* (10), 2507-2509.

158) Kim D.; Lee J.; Shim P.J.; Lim J.I.; Doi T.; KimKim S. *J. Org. Chem.* **2002,** *67* (3), 772-782.

159) Kornblum N.; Blackwood R.K.; Mooberry D.D. *J. Am. Chem. Soc.* **1956,** *78* (7), 1501-1504.

160) Kornblum N.; Larson H.O; Blackwood R.K.; Mooberry D.D.; Oliveto E.P.; Graham G.E. *J. Am. Chem. Soc.* **1956,** *78* (7), 1497-1501.

161) Kornblum N.; Eicher J.H. *J. Am. Chem. Soc.* **1956,** *78* (7), 1494-1497.

162) Maiti D.; Bhattacharya P.K. *Synlett* **1998,** (4), 385-386.

163) Campbell S.F.;Jaxa-Chamiec, A.A.; Roberts D.A. Cardiac stimulating cyclic sulfonamido substituted 4-piperidino-quinazoline derivatives, compositions, and method of use therefore. U.S. Patent 4542132, July 31, 1984.

164) Rathore R.; Kochi J.K. *J. Org. Chem.* **1996,** *61* (2), 627-639.

165) Urbanski T. *Chemistry and Technology of Explosives Volume 1;* Pergamon Press: Oxford, 1964 pp 589–594.

166) Dampawan P.; Zajac W.W. *J. Org. Chem.* **1982,** *47* (7), 1176-1181.

167) Rasmussen J.K.; Hassner A. *J. Org. Chem.* **1974,** *39* (17), 2558-2561.

168) Kizil M.; Murphy J.A. *Tetrahedron* **1997,** *53* (49), 16847-16858.

169) Stork G.; Sher P.M. *J. Am. Chem. Soc.* **1986,** *108* (2), 303-304.

170) Seyferth D.; Yamakazi H.; Alleston D.L. *J. Org. Chem.* **1963,** *28* (3), 703-706.

171) Heiba E.I.; Dessau R.M.; Koehl W.J. *J. Am. Chem. Soc* **1968,** *90* (21), 5905-5906.

172) Demir A.S.; Emrullahoglu M. *Curr. Org. Synth.* **2007,** *4* (3), 223-237.

173) Snider B.B. *Tetrahedron* **2009,** *65* (52), 10738-10744 and references therein.

174) Fristad W.E.; Peterson J.R. *J. Org. Chem.* **1985,** *50* (1), 10-18.

175) Hessel L.W.; Romers C. *Recl. Trav. Chim. Pays-Bas.* **1969,** *88* (5), 545-552.

176) Li J.J.; Corey E.J. *Name Reactions for Functional Group Transformations*; John Wiley & Sons: Hoboken NJ, 2007, pp 129-150.

177) Gololobov Y.G.; Zhmurova I.N.; Kusukhin L.F. *Tetrahedron* **1981,** *37* (3) 437-472.

178) Gololobov Y.G.; Kusukhin L.F. *Tetrahedron* **1992,** *48* (8), 1353-1406.

179) Alajarin M.; Conesa C.; Rzepa H.S. *J. Chem. Soc., Perkin Trans. 2* **1999,** (9), *1811-1814.*

180) Tian Q.W.; Wang Y.A. *J. Org. Chem.* **2004,** 69 (13), 4299-4308.

181) Huisgen R. *Angew. Chem., Int. Ed.* **1963,** *2* (10), 565-632.

182) Sustman R. *Pure Appl. Chem.* **1974,** *40* (4), 569-593.

183) Coldham I.; Hufton R. *Chem. Rev.* **2005***,* 105 (7), 2765-2810 and references therein.

184) Gallop M.A.; Peng G.; Sohn A. *J. Org. Chem.* **1999,** *64* (22), 8342-8349.

185) Kelly, T.R.; Ross; Schmidt T.E.; Haggerty J.G. *Synthesis* **1972,** (10), 544-555.

186) Hoye T.R; Hanson P.R.; Vyvyan J.R. *J. Org. Chem.* **1994,** *59* (15), 4096-4103.

187) Hoye T.R.; Zhao H. *J. Org. Chem.* **2002,** *59* (12), 4014-16.

188) Reich H.J *AX and AB Spectra* http://www.chem.wisc.edu/areas/reich/nmr/05-hmr-10-ax-ab.htm (Accessed 21/8/12).

189) Hatch L.F.; Li T.P. *J. Org. Chem.* **1963,** *28* (9), 2400-2403.

190) Lycan W.H.; Adams R. *J. Am. Chem. Soc.* **1929,** *51* (2), 625-629.

191) Chapuis C.; Robvieux F.; Cantatore C.; Saint-Léger C.; Maggi L. *Helv. Chim. Acta.* **2012**, *95* (3), 428-447.

192) Commercially available compound. ^{1}H and ^{13}C spectra downloadable from Aldrich website http://www.sigmaaldrich.com/spectra/fnmr/FNMR002058.PDF (accessed 20/9/12).

193) Commercially available compound. ^{1}H and ^{13}C spectra downloadable from Aldrich website http://www.sigmaaldrich.com/spectra/fnmr/FNMR009367.PDF (accessed 20/9/12).

194) Mukaiyama T.; Izumi J.; Miyashita, M.; Shiina I. *Chem. Lett.* **1993**, *22* (5), 907-910.

195) Mizuno T.; Nakai T.; Mihara M. *Synthesis* **2010,** (24), 4251-4255.

196) Armarego W.L.F.; Chai C.L.L *Purification of Laboratory Chemicals 5th Ed;* Elsevier Science: USA, 2003, p 484.

197) Amberlyst™-15 Dry Product Data Sheet IE-520; Rohm & Haas:Philadelphia PA, August 2005
http://www.amberlyst.com/literature/us/15dry.pdf
(Accessed 4/12/11; widely downloadable from other suppliers of this resin.)

198) *Encyclopedia of Reagents for Organic Synthesis Vol 8;* Paquette L.A. Ed.; John Wiley & Sons, Chichester,1995, pp 5536-5539.

199) Pray A.R. Anhydrous Metal Chlorides. In *Inorganic Syntheses Vol 28*; Angelici R.J. Ed.; John Wiley & Sons: Chichester, 1990, pp 321-323.

200) *Organic Syntheses*; Wiley & Sons: New York, VI, 1988; pp 220-223.